THE American Journal OF Gastroenterology

VOL. 28, NO. 6 DECEMBER, 1957

The Treatment of Pseudocysts of the Pancreas

The Association of Duodenal Diverticula with Pancreatic Disease, with Special Reference to Carcinoma of the Pancreas

The Use of Radioactive Rose Bengal as a Test in the Differential Diagnosis of Jaundice

Hexocylium Methosulfate, a New Anticholinergic: Some Clinical Impressions

Clinicopathological Conference

Twenty-third Annual Convention
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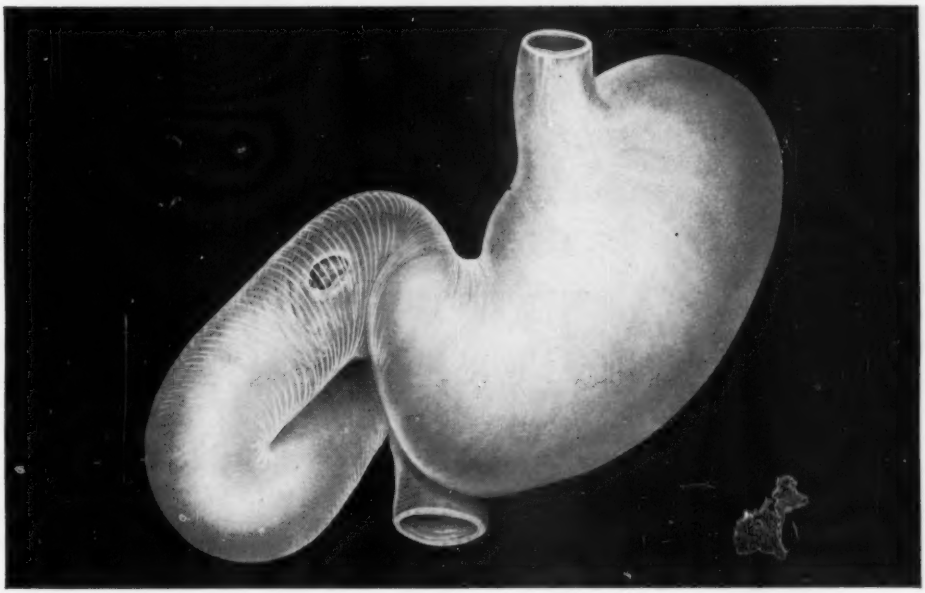

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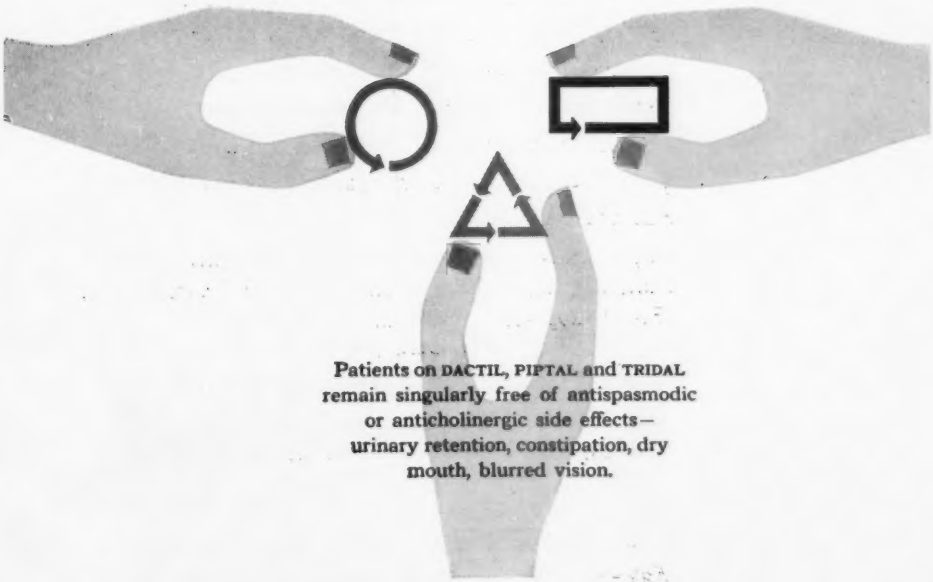

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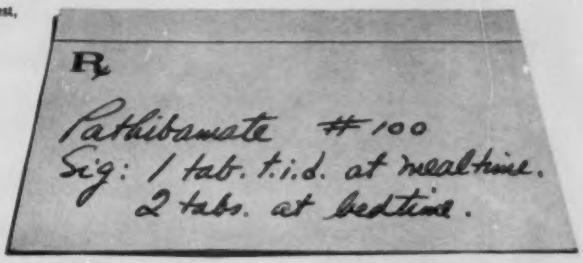

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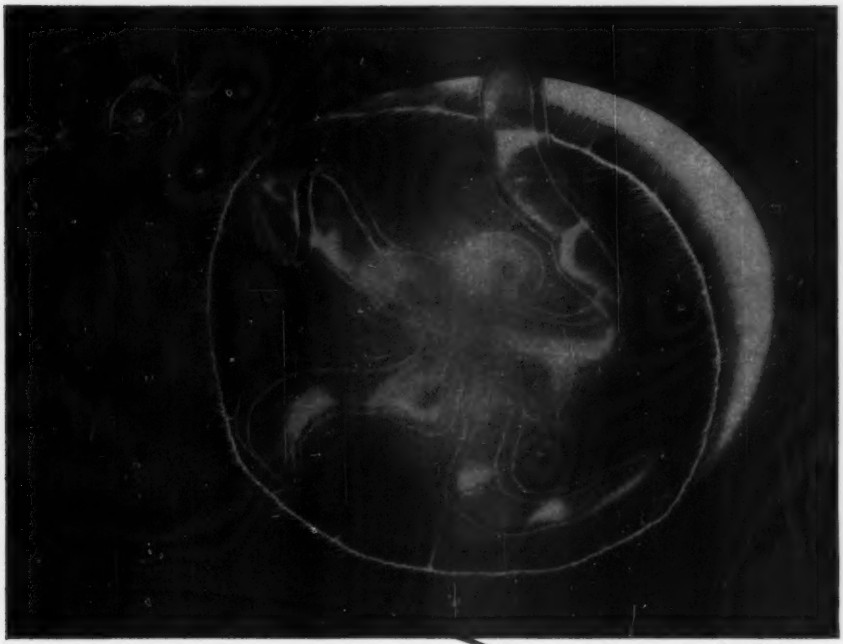

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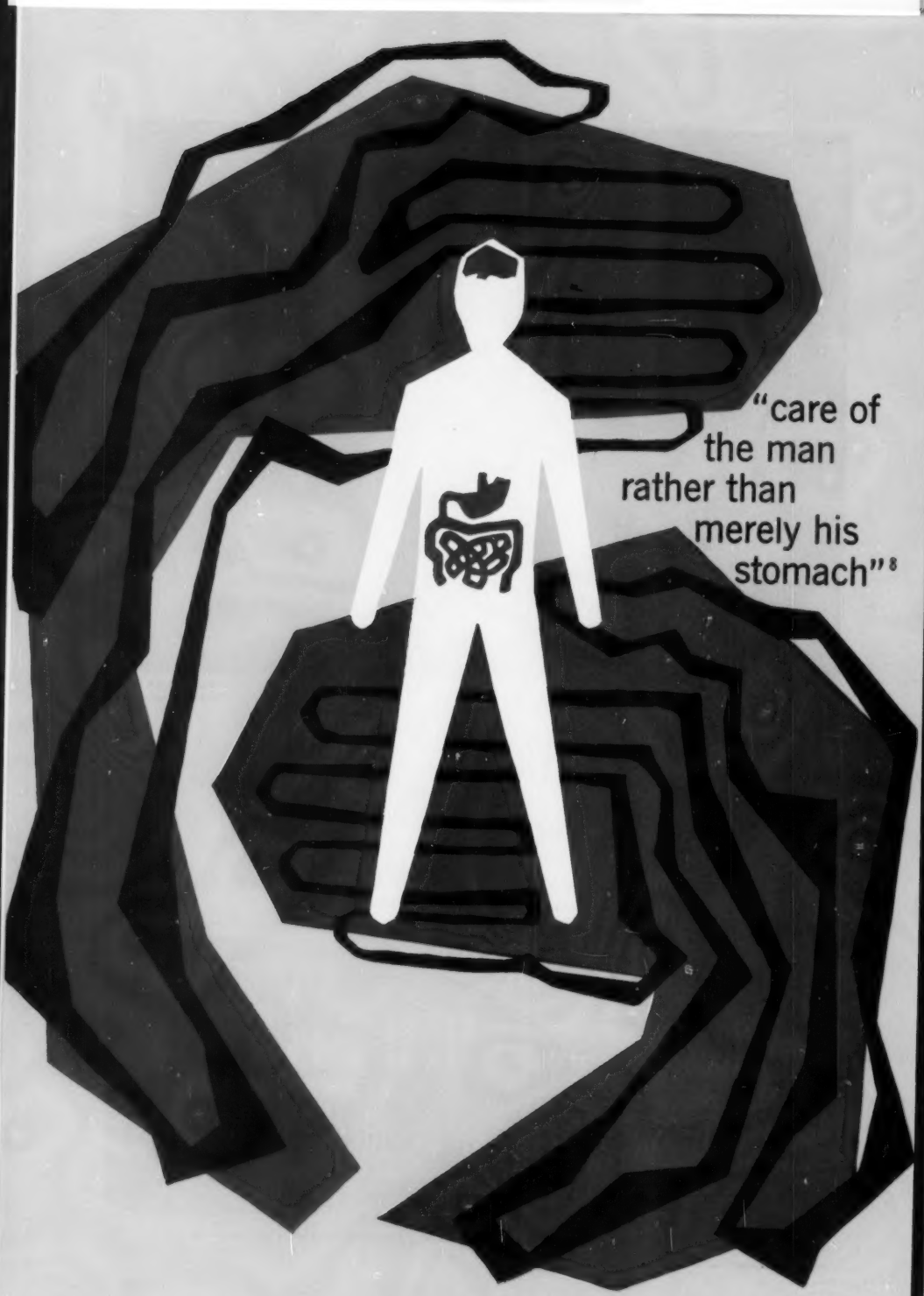
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VOLUME 28 DECEMBER, 1957 NUMBER 6

THE TREATMENT OF PSEUDOCYSTS OF THE PANCREAS

JOSEPH M. MILLER, M.D.
MILTON GINSBERG, M.D.
and
JOHN A. SURMONTE, M.D.*
Ft. Howard, Md.

The increasing frequency with which pseudocysts of the pancreas are being seen indicate that they are not the rarely occurring lesions they have been considered previously. Surgeons, in private practice in smaller communities, however, will not see many patients with this condition. The treatment of pseudocyst is reviewed because surgical management has changed since operation for pseudocyst was first done.

The term, pseudocyst of the pancreas, is reserved for a cystic lesion which follows acute inflammation and is usually located in the omental bursa. Grossly, differentiation from a true pancreatic cyst may be difficult[33]. Pseudocysts are usually unilocular and surrounded by a fibrous capsule in which the changes of chronic inflammation are found. The true pancreatic cyst may be multilocular with a lining of cuboidal or columnar epithelium, which, however, is frequently absent[32]. The color of the liquid in the pseudocyst may vary from a thin straw to a thick dark brown. Enzymes are found in about 75 per cent of the cysts[25,31].

Trauma to the abdomen has been reported to be the etiologic factor in from 1 to 51 per cent of pseudocysts[6,11]. The pancreas is compressed between an applied force and the upper lumbar vertebrae. The injury usually occurs in the body of the gland and less frequently involves the head of the pancreas[8]. A tear in the capsule of the gland or a small area of hemorrhagic necrosis with extravasation of the pancreatic enzymes results. The enzymes produce a chemical peritonitis in the omental bursa. The foramen of Winslow may become occluded and fluid may accumulate in the lesser peritoneal sac[9]. More commonly

*Surgical Service, Veterans Administration Hospital, Ft. Howard, Md.

the development of a pseudocyst is preceded by an attack of acute or recurrent pancreatitis. The cysts form in a few days to several months. Associated biliary tract disease has been reported to be present in about 30 per cent of the patients with pseudocysts of the pancreas[25]. The cyst may become markedly adherent to the pancreas, transverse colon, stomach, duodenum, common bile duct, or other contacting organs. The lesion may present through the gastrocolic omentum, the gastrohepatic omentum, the transverse mesocolon, or between the layers of the transverse mesocolon[37]. Ormond, Wadsworth, and Morley[29] re-

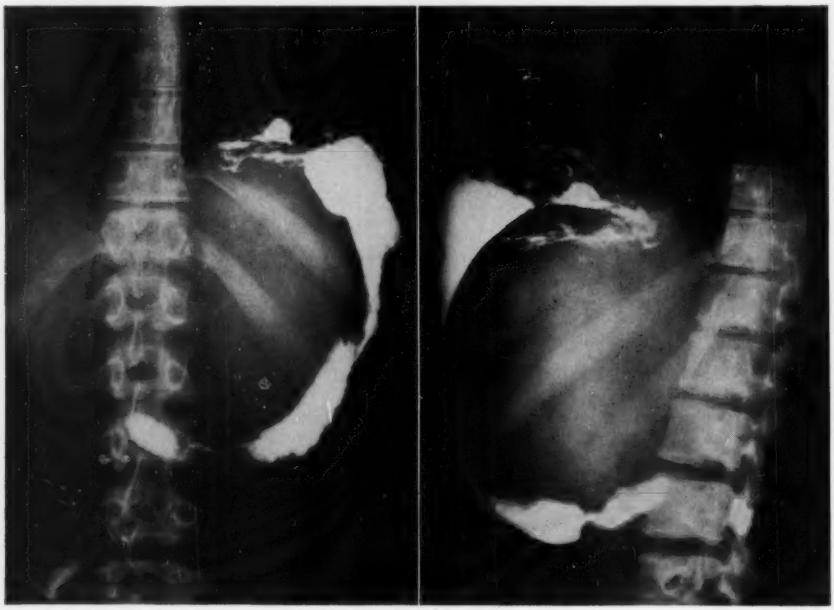

Fig. 1 Fig. 2

Fig. 1—Anterior-posterior view of the abdomen after ingestion of barium showing lateral displacement of the stomach.

Fig. 2—Right posterior oblique view of abdomen after ingestion of barium showing anterior displacement of the stomach.

ported a cyst originating in the head of the pancreas and spreading to the bed of the right kidney, displacing it toward the midline and downward. Chodoff[10] related details of a patient in whom a pseudocyst developed in the region of the head of the pancreas ten days after marsupialization of a large cyst in the region of the body of the pancreas. Evans, Lubben and Whigham[15] cited a case in which the fluid removed from a pseudocyst contained ova of *Ascasis lumbricoides* and postulated that the cyst formed from a necrotic parasitic area in the body or tail of the pancreas.

Patients with pseudocysts comprise about 0.001 per cent of admissions to the hospital[11]. Pseudocysts constitute about 40 per cent of all pancreatic cysts[2], are found about equally in men and women[5], and occur predominantly between 20 and 60 years of age[25]. A racial predilection has not been noted[27]. The condition is rarely seen in children[27]. Mithoefer[28] reported an instance in a 20-month-old girl and Railton[36], Telling and Dobson[45], and Ehla[14] described pseudocysts in children.

The patient with a pseudocyst of the pancreas usually complains of a mass and vague discomfort in the upper abdomen, and nausea and vomiting[12]. A history of recent loss of weight can commonly be obtained. The patient may give a history suggestive of acute or recurrent attacks of pancreatitis or of abdominal trauma. In the present series of patients with pseudocysts of the pancreas, a history of chronic alcoholic intoxication was usually obtained. Occasionally, the lesion may be discovered during an examination for an unrelated

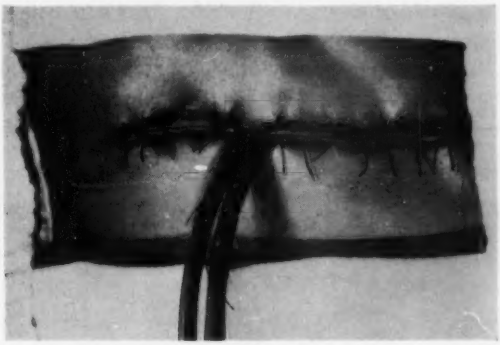

Fig. 3—Appearance of operative wound following marsupialization and placement of two number 18 French catheters for air-vent suction.

condition. The onset of jaundice may cause the patient to seek medical attention.

The routine hemogram and urinalysis are not significantly altered. The determinations of the blood sugar usually are normal. The serum amylase level usually is elevated when the patients present themselves at the hospital during a recurrent attack of acute pancreatitis. Roentgenograms of the abdomen show the shadow of a soft tissue mass in the epigastrium or the left hypochondrium. Following the ingestion of a barium meal, roentgenograms may demonstrate a smooth, rounded extrinsic defect on the posterior wall of the stomach with resultant anterior displacement. Either the lesser or the greater curvatures may be displaced. The duodenal loop may be widened. The barium enema may show displacement of the transverse colon anteriorly and caudally. Rarely, displacement of the right or the left kidney and ureter may be seen with pyelographic studies.

Pseudocysts of the pancreas must be differentiated from other cysts of the pancreas, omental cysts, mesenteric cysts, renal cysts, renal tumors, retroperitoneal tumors, ovarian cysts and tumors of the liver, spleen, and gastrointestinal tract. Ormond, Wadsworth, and Moreley[29] reported three patients in whom urologic diagnoses were entertained.

Complications of pancreatic pseudocysts occur infrequently. Traumatic or spontaneous rupture is the most serious. Rose[38], in reporting spontaneous rupture through the gastrocolic omentum into the free peritoneal cavity, described the occurrence of acute severe abdominal pain, the sudden disappearance of the mass, and the presence of vomiting in the patient. Profound shock and generalized peritonitis were present. The serum amylase was greatly elevated. The mortality associated with this complication is very high. Management of the patient with perforation of a pseudocyst into the free peritoneal cavity includes treatment of the shock and then marsupialization of the cyst. Koucky[21] reported six cases of perforation with four deaths. The cyst may also perforate spontaneously into a segment of adherent gastrointestinal tract. The patient reports a sudden disappearance of the abdominal mass followed by diarrhea. Expectant treatment is indicated in such patients since the spontaneously established cystoenterostomy may lead to a cure.

A left pleural effusion complicating pseudocysts was reported in two cases by Bickford[3], and in a third patient by Cross, Null and Loeb[16]. It is conceivable that such effusion may have been the result of thoracic contusion from the same injury causing formation of the cyst. In 1951, Edlin[13] reported autopsy findings of a large posterior mediastinal cyst which communicated with a pseudocyst in the lesser peritoneal sac through the esophageal hiatus. Pseudocysts of the pancreas may also become calcified[30].

Although the treatment of pseudocysts of the pancreas has varied in recent years, the basic principal has been eradication of the cyst by drainage. If treatment is not given, the lesion will produce a state which is incompatible with life and the general condition of the patient will gradually deteriorate[7]. Brunschwig[7] reported that late in the nineteenth century aspiration of the cyst was performed, but rapidly proved to be an inadequate form of treatment. Open drainage of a pseudocyst through a left lumbar incision also has been performed but the operation is technically difficult and the exposure is poor[7]. Bozeman[4] in 1882, was the first to excise such a lesion. This procedure definitely is desirable but usually not practical since the tedious excision may be associated with a not insignificant risk of injury to surrounding structures and complicated by annoying hemorrhage[1]. In 1883, Gussenbauer[18] was the first surgeon to marsupialize a pseudocyst to the anterior abdominal wall. This procedure has remained a favorite with many surgeons[2,19,35]. The associated complications are a persistent draining fistula, infection of the cyst, and hernia. Jedlicka[20], in 1923, successfully made an anastomosis between a cyst and the stomach to

produce internal drainage and thus obviate the possibility of an external fistula. Since then other forms of internal drainage utilizing the gallbladder or jejunum[26] have been used. Cystogastrostomy may be objectionable because of the possibility of regurgitation and retention of stomach contents in the cyst[22]. Maxeiner and Maxeiner[24] have reported a peptic ulcer occurring at the site of anastomosis. Transgastric pancreatocystojejunostomy has been recommended as a satisfactory operation[41]. Cholecystocystostomy has not led to efficient evacuation of the cyst. In recent years cystojejunostomy using the Roux-en-Y technic has become the procedure of choice in many quarters[17,27,34,39,42]. This procedure may be complicated by digestion of the suture at the anastomosis with resultant leakage or premature closure of the stoma with recurrence of the cyst[44,46].

Case Report

A 26-year old Negro man was admitted to the Veterans Administration Hospital, Ft. Howard, Md., on 19 November 1953 with the chief complaints of pain and swelling of the abdomen of about nine days' duration. There was associated anorexia and a moderate degree of vomiting. The patient had lost about ten pounds in weight during the past year but most of it was lost recently. He had been admitted to the hospital on 12 January 1953 with diagnosis of acute gastritis, cirrhosis of the liver, and chronic alcoholism. On 22 February 1953, he was admitted for chronic pancreatitis, cirrhosis of the liver, and chronic alcoholism. During this admission, the serum amylase was 258 Somogyi units per 100 c.c. as contrasted to a normal value of 80.

The patient was acutely ill, cachectic, and dehydrated. A large tender epigastric mass extended from the xiphoid process to the umbilicus.

The hemogram and the urinalysis were normal. Roentgenograms of the abdomen revealed a large round homogenously dense mass in the epigastrium. Following a barium meal, roentgenograms showed the stomach to be displaced laterally and anteriorly by the mass (Figs. 1 and 2). The passage of barium through the pylorus was delayed.

On 24 November 1953, laparotomy was done through a transverse upper abdominal incision. A large cyst, from which 2,100 c.c. of machine-oil-like brown fluid were aspirated, occupied the omental bursa. A part of the wall was removed for biopsy. Marsupialization was done through the gastrohepatic omentum and two number 18 French rubber catheters were placed within the cavity for air-vent suction drainage (Fig. 3).

On 27 November the drainage was minimal. The catheters were removed on 3 December. The wound was healed on 5 January 1954. The tissue removed at operation was subacutely inflamed scar tissue. The patient began to eat well

and gain weight. He was discharged from the hospital on 5 January 1954. A communication from the patient on 18 December 1954 indicated that he was in good health and had not had a recurrence of the pseudocyst.

Comment

Marsupialization has proved to be a satisfactory method of treatment for seven of the nine patients with pseudocysts of the pancreas (Table I). Three cysts were packed and the remainder were treated with air-vent suction. This method of suction has been very efficacious in keeping the wound dry. Two number 18 French rubber catheters were placed in the cyst after the wall had been sutured to the anterior parietal peritoneum. The incision was closed about the catheters. A Stedman pump provided the necessary suction. The second catheter acted as an air-vent for the system. With this method of treatment, the cysts became obliterated more rapidly and healing of the wound was hastened. Drainage from the cyst usually decreased rapidly. Digestion of the skin was not seen. On about the twelfth postoperative day, removal of the catheters was started and completed in several days.

In seven patients, healing was obtained on the average, in about 37 days. In two patients, a persistent fistula followed marsupialization. The reduced incidence of fistula in this group of patients as compared to similar groups may be due to the early use of air-vent suction. In one patient an anastomosis of the fistula to the jejunum according to the method of Roux was made successfully. The fistula in the second patient closed spontaneously after a prolonged period. A postoperative hernia was noted in two patients and in one of these, twice.

Follow-up of the patients has ranged from ten months to five and one-half years. A recurrence of a pseudocyst has not been seen and new cysts have not formed. All wounds have remained healed. Four patients have been readmitted to the hospital for exacerabations of the pancreatitis due to acute and chronic alcoholism. Conservative treatment resulted in relief of symptoms in all.

It is essential that drainage, either external or internal, be provided for patients with pseudocysts of the pancreas. A routine operation cannot be outlined. The procedure must be fitted to the stage of the disease encountered when operation is done. The poor condition of the patient, evidence of acute inflammation in the wall of the pseudocyst or a thin wall of the pseudocyst contraindicate the performance of anything but the simplest procedure which is marsupialization. The complications of this operation are the formation of a fistula, excoriation of the skin of the wall of the abdomen, premature closure of the fistula with reformation of the cyst, alternating periods of drainage, and cessation of drainage associated with pain and apparent redistention of the pseudocyst[42].

TABLE I

Number of case	Serum Amylase Somogyi units*	Date of marsupialization	Air-vent suction	Persistent Fistula	Digestion of skin	Date wound healed	Hernia	Recurrence of pancreatitis
1	170	1 Nov. 1948	Yes	No	No	24 Nov. 1948	Yes, twice	Yes
2	208	24 Feb. 1949	No	No	No	19 Mar. 1949	No	Yes
3	235	9 Dec. 1949	No	No	No	13 Jan. 1950	No	Yes
4	227	17 Nov. 1950	Yes	No	No	9 Jan. 1951	Yes	Yes
5	—	13 Mar. 1953	No	No	No	18 May 1953	No	No
6	262	26 Aug. 1953	Yes	Yes	No	14 Feb. 1954	No	No
7	147	25 Sep. 1953	Yes	No	No	30 Oct. 1953	No	No
8	—	24 Nov. 1953	Yes	No	No	14 Dec. 1953	No	No
9	79	18 June 1954	Yes	Yes	No	Late in Dec., 1954	No	No

*The normal value for the serum amylase at the Veterans Administration Hospital, Ft. Howard, Md., is 80 Somogyi units per 100 c.c.

Rossing[40] reported that the mortality from marsupialization was about 4.5 per cent. Morbidity and mortality would be considerably less, however, in a comparable series of patients subjected to operation at the present time because of the improvement made in the care of the patients. In about 50 per cent of the patients who have a marsupialization, a fistula will occur[23]. Spontaneous closure of the fistula occurs rapidly in 50 per cent of these patients. The incidence of fistula, moreover, can be reduced considerably by providing air-vent suction of the pseudocyst at the time of marsupialization.

Late in the course of a patient with a pseudocyst of the pancreas, the patient will be in better condition, the acute inflammatory process will have subsided and the wall of the pseudocyst will be thicker, so that anastomosis of the pseudocyst to the upper part of the jejunum according to the method of Roux may be done. Shumacker[43] has collected a series of 17 patients with a pseudocyst, including personal observations, who have had such an operation done successfully without mortality or morbidity.

The condition of the patient, the status of the pseudocyst, and the experience of the surgeon, however, must be considered in the choice of the operation. In a patient in poor physical condition, an anastomosis between an inflamed pseudocyst and the jejunum may be a troublesome procedure associated with mortality and morbidity for the surgeon who has had little experience with this condition. This operation cannot always be recommended in patients in whom excision is not technically feasible or seems hazardous. The bad features of marsupialization have been exploited but they rarely endanger life. A leak in a cystojejunostomy is a serious accident. A successful result has been reported in 17 patients[43] but reports of unsuccessful results are usually not made. Numerous surgical procedures have enjoyed transient popularity in the treatment of pseudocysts. An ideal operation to suit all situations has not been described. It would seem advisable for the surgeon to do the procedure which would most likely benefit the particular patient. In general, the surgeon will find marsupialization to be the safest procedure unless patient, pseudocyst, and surgeon fulfill certain qualifications.

Summary

Pseudocysts of the pancreas were reviewed and the details of nine patients with this condition were reported. The operation must be chosen to fit the conditions present in the individual patient. The safest procedure for routine use is marsupialization but anastomosis to the jejunum may be employed if the condition of the patient, the character of the pseudocyst, and the experience of the surgeon permit.

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THE ASSOCIATION OF DUODENAL DIVERTICULA WITH PANCREATIC DISEASE, WITH SPECIAL REFERENCE TO CARCINOMA OF THE PANCREAS

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There have been few casual references in the literature regarding the association of duodenal diverticula with pancreatic disease. Although the association of these conditions is mentioned in the literature by some authors, illustrations in many were lacking. My interest in this topic was stimulated by our experiences in a number of instances of duodenal diverticula associated with carcinoma of the pancreas, and also by the difficulty in obtaining references to this dual condition in the literature. From a perusal of the literature it seems that the effect of pancreatic disease upon duodenal diverticula has not been deemed of sufficient importance to merit more than a passing notice. A study of these conditions is therefore of interest, and more objective information needs to be collected. This paper is therefore designed to emphasize the roentgenologic importance of noting the effect of the pancreas upon duodenal diverticula and warrants a brief communication.

The true incidence of duodenal diverticula has not been established because of the difficulty of demonstrating all the diverticula, not only by roentgen examination, but also at autopsy. This is due to the fact that many diverticula do not fill with opaque media during the examination or that they are empty at the time of the examination or are overshadowed. They are also difficult to find at autopsy because of their intimate location with the pancreas and the difficulty of recognizing them when the duodenum is undistended. The roentgen incidence of duodenal diverticula has been variously reported to occur between 0.02 and 5.7 per cent, while the autopsy incidence is about 0.6 per cent. When, however, the duodeni are more thoroughly examined at autopsy the incidence increases greatly. Ackermann, in a meticulous study of 50 cadavers found 11 with a duodenal diverticulum, an incidence of 22 per cent. All of these were observed on the concave border of the duodenum, and many of them were found to be embedded in the pancreas.

Most diverticula of the duodenum occur on the concave border of the second portion and lie in close contact or embedded into the head of the pancreas. Of Ackermann's 11 cases, all but 4 were buried in the substance of the pancreas. In 43 cases, Kellogg and Kellogg found that 23 penetrated the head of the pancreas, 14 extending behind, 2 extending in front and 4 extending towards the head of the pancreas. The intimate relationship of the location of duodenal diverticula to the pancreas accounts for the frequent failure of the surgeon to see these pouches at operation, even after they have been demonstrated by roentgen examination. In 25 surgical cases for the removal of duodenal divertic-

ula, Cattell and Mudge found 6 to be intimately associated with the pancreas, and in 3 of these there was actual embedding of the pouch within the pancreatic substance.

The true incidence of the coexistence of duodenal diverticula with carcinoma of the pancreas has not been established. The impression is gained from a perusal of the literature that the association of these two conditions is comparatively rare. But contrary to the prevailing impression, it would seem from a study of anatomic findings that since diverticula of the duodenum are commonly imbedded in the pancreas, the association of duodenal diverticula and carcinoma of the head of the pancreas must occur with greater frequency than one

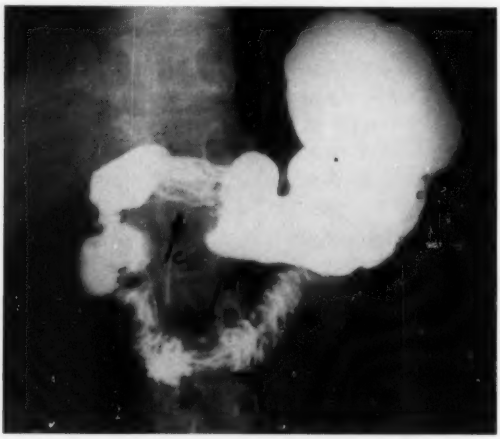

Fig. 1—The prone roentgenogram showed a large diverticulum at arrow A: because of its posterior rotation, this diverticulum is overshadowed by the descending duodenum. A smaller diverticulum is noted at arrow B, on the concave border of the third portion of the duodenum. A pressure defect is shown at arrow C, in the pylorus. The reversed inverted-3 filling defect shown at arrow D, was produced by enlargement of the head of the pancreas. Note also the absence of enlargement of the duodenal loop.

is led to believe from any impression gained from the literature. In order to determine the incidence of the dual conditions, 72 cases of carcinoma of the pancreas were collected, which were confirmed by operation or at autopsy and who had had gastrointestinal roentgen studies. Of these, 4 revealed the presence of duodenal diverticula in the second portion of the duodenum, giving an incidence of the coexistence of the dual conditions of 5.5 per cent.

In a review of the literature from 1930 to 1957 there have been about 20 cases of duodenal diverticula associated with carcinoma of the pancreas either mentioned or reported to which an additional case is herein reported by the author. Cases of carcinoma of the pancreas with duodenal diverticula have been

reported by Möhlmann, Friedman, Chitamber, Gil et al., Strode, Saupe, Schaefer, and others. Ochsner mentions 3 instances, and in addition he illustrates a case belonging to Dr. J. Richards Aurelius.

Occasionally a pseudodiverticulum of the duodenum may be produced by an ulcerating perforating carcinoma of the head of the pancreas. These diverticula closely simulate true diverticula. Herrnheiser, and Abrams, each reported such an instance.

The following case is a representative example of a carcinoma of the pancreas associated with a duodenal diverticulum in which the descending duodenum was rotated.

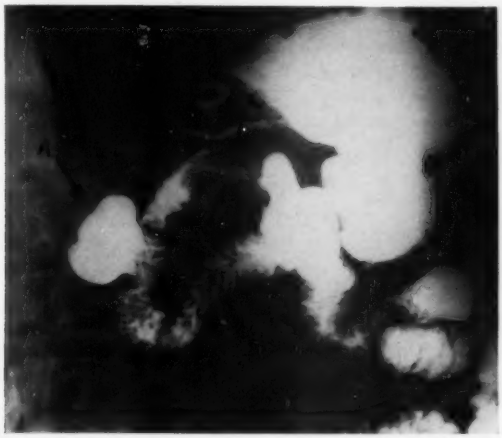

Fig. 2—Right oblique roentgenogram of same case. The posterior position of the large diverticulum in the descending duodenum is shown at arrow A. The smaller diverticulum is observed in the third portion of the duodenum. The pyloric defect is shown at arrow C; note the intact mucosal markings in the pylorus, indicating evidence of extrinsic pressure.

Case Report

Female, aged 58, suffered an acute attack of gallstones for which she was operated on. Following the operation she complained of pains across the upper abdomen which radiated to the mid-back and shoulder blades. Eight months later a gastrointestinal roentgen examination revealed the following changes. The prepylorus showed a narrowing resulting from pressure. A large duodenal diverticulum in the second portion was demonstrated, which appeared to be rotated with the duodenum, so that the diverticular pouch appeared to be on the outer convex aspect instead of being on the concave inner border. Another smaller diverticulum, about the size of a pea, was seen in the third portion of the duodenum. In addition, an inverted-3 defect was observed with the larger

diverticulum on the outer aspect of the duodenum, its position being due to the rotation of the descending duodenum. Besides the roentgenologic findings, a sense of resistance, as if there was a mass present, was felt in the epigastrium. On deep palpation, pain was elicited over this area, which simulated the pain and discomfort the patient complained of. Even though there was no evidence of displacement or enlargement of the duodenal loop, on the basis of the above findings a pancreatic lesion was suspected and a suggestive diagnosis of carcinoma of the pancreas was made. At operation an extensive carcinoma of the pancreas with metastasis was found and was confirmed at autopsy.

The incidence of the association of pancreatitis with duodenal diverticula has not been established. In 26 postmortem examinations, Demole and Aziz found 3 instances of pancreatitis associated with duodenal diverticula, an incidence of 11.5 per cent. There have been a number of publications on pancreatitis involving duodenal diverticula. Attention has been directed to the frequent association of pancreatitis with duodenal diverticula by Edwards, Fulde, Siehe, and others. In most instances the pancreatitis results from inflammatory changes of diverticula, perforation of a diverticulum or to pressure of the diverticulum upon the pancreatic duct. Ogilvie, who reported 4 cases of duodenal diverticula associated with pancreatitis, pointed out that pressure of a pre-Vaterian diverticulum upon the pancreatic duct at the ampulla of Vater may be the cause of pancreatic disorder. Case noted the frequent coexistence of chronic pancreatitis with duodenal diverticula. Poppel illustrated 2 instances, and Lucinian reported a case of pancreatitis resulting from a perforation of a duodenal diverticulum. Cases of the dual conditions have been reported by Svartz and Sjoberg, Sokól, and others.

Necrosis of the head of the pancreas may result from pressure of a duodenal diverticulum obstructing the pancreatic duct. Ogilvie reported 4 cases, and Wilkie 1 case of this condition. Hodes et al. called attention to the occasional presence of false diverticula resulting from necrosis and ulceration of a malignant tumor which communicates with the lumen of the duodenum.

The roentgen examination affords the one sure means of demonstrating in most instances the duodenal diverticulum, which might yield information regarding the presence of a carcinoma of the head of the pancreas. Specific attention must be focused upon the changes observed in the position, shape and direction, noting for distortion and pressure of the duodenal diverticulum. The role played by changes in the diverticulum as a diagnostic sign of a pancreatic lesion has not been sufficiently stressed. It must also be emphasized that the importance of the roentgen examination does not rest only on its ability to demonstrate the diverticulum, but it is essential to properly interpret the changes and correlate them with the clinical data. The roentgen manifestations are more or less easily detected when a diverticulum is shown coexisting with enlargement of the head of the pancreas. Often the diverticulum is displaced

upward, either anteriorly or posteriorly. The sac may also show signs of pressure with flattening of its surface. On close observation of the duodenum, the mucosal folds are shown to be distorted, disoriented and at times rotated. An inverted-3 filling defect may be demonstrated in some instances. Frostberg and Feldman and others have directed attention to this sign as indicating evidence of pressure from the pancreas and other enlargements occurring in the duodenal loop area. Occasionally there is a rotation of the descending portion of the duodenum and the diverticulum may appear to be directed from the outer convex border instead of from the inner concave border of the duodenum. The inverted-3 defect may likewise appear to be in a similar position as a result of rotation due to pressure from enlargement of the head of the pancreas. Friedman reported such a case, and another case is reported in this communication.

Summary

Duodenal diverticula are often embedded into the head of the pancreas. These diverticula may not always be demonstrated even at surgery or at autopsy, unless they are especially sought after. Duodenal diverticula are not infrequently involved in association with pancreatic disease. Up to the present time the incidence of involvement and association of duodenal diverticula with pancreatic disease has never been established. In order to determine the incidence of the dual conditions, 72 cases of carcinoma of the pancreas were collected and of these 4 revealed the presence of a duodenal diverticulum, an incidence of 5.5 per cent. A review of the literature revealed about 20 cases of the association of duodenal diverticula with carcinoma of the pancreas. There is no doubt that there must be many more such cases which have not been recognized. It is certain that if the dual conditions were diligently sought after, their incidence would be greatly increased. It is also emphasized that duodenal diverticula may be associated with pancreatitis and necrosis of the pancreas.

Attention is directed to the roentgenologic examination as a means of detecting changes occurring in duodenal diverticula as a diagnostic feature of pancreatic disease. A case is reported in which the duodenum and a duodenal diverticulum was rotated, so that the diverticulum appeared to arise on the convex border instead of the inner concave border of the duodenum. This rotation was produced by an extensive carcinoma of the pancreas.

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THE USE OF RADIOACTIVE ROSE BENGAL AS A TEST IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

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Recently Taplin and associates[1] introduced radioactive rose bengal as a substance to be utilized in testing liver function. Rose bengal, a dye, was used for many years to measure the excretory capacity of the liver[2]. The process of removal of rose bengal involves uptake and storage by the liver and transfer into the biliary tract. Certain factors of hepatic circulation and the intricate functional activities of the liver cells are recognized to influence the passage of rose bengal through the liver, but it is not the purpose of this study to evaluate the effect of these factors on the test *per se*. The introduction of I^{131} rose bengal permitted a means of determining the amount of dye taken up and excreted by the liver. This paper records the results of an investigation of patients with jaundice and was planned to determine if the radioactive rose bengal test could be a clinically useful procedure to differentiate obstructive from parenchymatous jaundice.

Method

Each patient was placed in the prone position with a small pillow beneath the head. The scintillation counter with lead collimator was placed over an area marked on the patient's chest midway between the mid-clavicular and anterior axillary line along the upper border of liver dullness, tilted at a 20° angle toward the chest and away from the gallbladder. A background count was taken over a three-minute period. The patient received by vein five microcuries of radioactive iodinated serum albumin (RISA), and three minutes later a count was taken for three minutes with the position of the counterhead and lead collimator unchanged. Five microcuries of radioactive rose bengal were then given intravenously. Thereafter, three-minute counts were taken at 15-minute intervals

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for a period of two to two and one-half hours. After each test a curve was constructed in which the ordinate represented by the number of counts per minute was plotted against the abscissa made up of the time in minutes.

A total of 36 patients were studied. Eighteen patients were considered to be free of liver disease by clinical evaluation and complete battery of liver function studies. A diagnosis of parenchymal jaundice was made by accepted clinical criteria in 12 patients. A liver biopsy was performed to confirm the diagnosis in nine of these patients. Of the patients with parenchymal jaundice

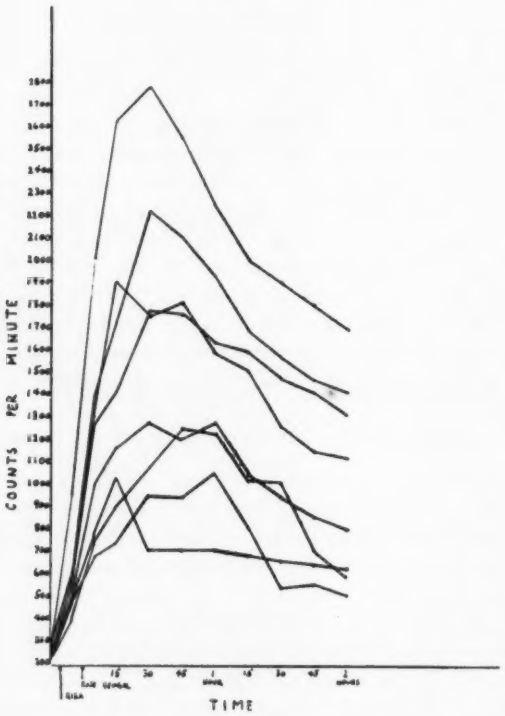

Fig. 1

seven suffered from portal cirrhosis, four had infectious hepatitis, and one was diagnosed as acute cholangitis with secondary hepatic involvement. Six patients with obstructive jaundice were studied. A diagnosis of carcinoma of the pancreas was made in three patients, choledocholithiasis in two, and acute pancreatitis with obstructive findings in one. All except the last were proven by surgical exploration. In all cases of jaundice, an attempt was made to perform the study before the jaundice appreciably diminished from its highest peak.

Results

Each of the curves was examined for the characteristics upon which the analysis was to be made: 1. Maximum peak of the curve. 2. Time required to reach the maximum peak. 3. Height of the curve at each 15-minute interval following the injection of rose bengal. 4. Contour of the curve. 5. Time required for the curve to return to the level which had been reached three minutes after the injection of rose bengal.

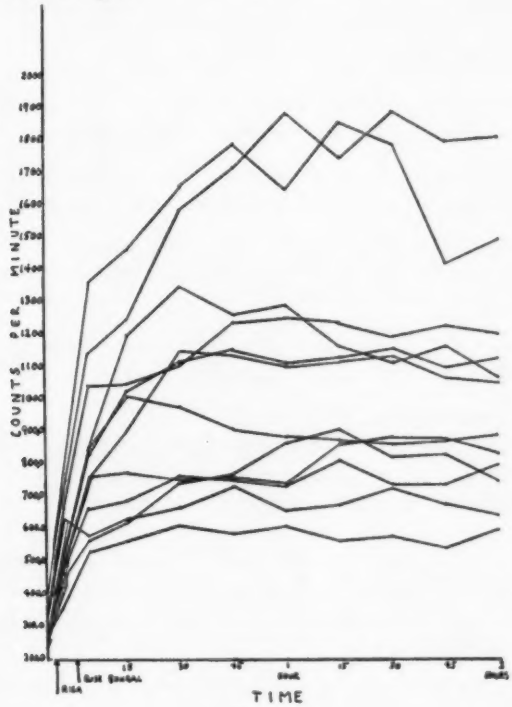

Fig. 2

Normal patients:—Eighteen individuals were studied who were considered to be free of liver diseases. Their acceptability as normal was based on history, and the physical examination and a battery of liver function studies whose results were within the accepted range of normal.

The curves of the 18 normal patients tested revealed the following features which were subsequently used to define a normal pattern:

1. The maximum peak of the curve in every patient occurred within 15 to 75 minutes after the injection of rose bengal.

2. At two hours every curve returned to levels below that obtained three minutes after the injection of rose bengal.

3. In 15 patients the curve showed a sharp and rapid rise to a peak and then a gradual decline. In 3 patients an irregular decline in the curve was noted.

Although the contours of the curves were similar, there was extremely wide individual variation in the number of counts per minute, at each 15-minute interval. For example, at 30 minutes after rose bengal was administered, the range in counts per minute was from 760 to 2,500. Also, the maximum peak of the individual curve showed extremely wide variation (Fig. 1).

The height of the maximum peak was related to height, weight and surface area. In each instance there was little correlation to be found.

Hepatocellular jaundice:—Curves were established for 12 patients with hepatocellular jaundice. The following observations were made:

1. In 11 of 12 cases, retention of the dye was noted so that the level of the curve at two hours remained higher than the level three minutes after the injection of rose bengal.

2. In 2 of the 12 patients the maximum peak was reached after 75 minutes, the time which had been selected as the upper limit of normal.

3. As in normal patients, great variations were found in amplitude at any given time after the injection of rose bengal. For example, at 30 minutes after the injection of the dye 2 patients had 600 to 700 counts per minute, while 2 patients had 1,600 to 1,700 counts per minute, and the remainder were scattered between these extremes. The maximum peak of the individual curves also showed the same wide variations. Attempts to correlate the maximum peak of the curve with height, weight, surface area and degree of jaundice again disclosed poor correlation. The wide variation in the amplitude of the curves at any given time is illustrated in Figure 2.

Obstructive jaundice:—Curves were constructed for 6 patients with obstructive jaundice. The following results were observed.

1. In all 6 patients retention of the dye was noted so that the level of the curve at two hours was higher than the level obtained three minutes after the injection of rose bengal.

2. In 3 of 6 patients the time at which the maximum peak of the curve was reached exceeded 15 minutes.

3. As in normal and patients with hepatocellular jaundice great variations were noted in the amplitude of the curves at any given time after the injection of rose bengal. This is illustrated in Figure 3. The same wide variations were found in the maximum peak of the individual curve. Again there was poor cor-

relation with height, weight, surface area and degree of jaundice when compared to a characteristic curve pattern.

Comparison of cases of parenchymatous and obstructive jaundice:—When average curves of normal individuals were compared with curves of patients with jaundice (Fig. 4), it was found that icteric patients showed decreased uptake of the dye. The decreased uptake of dye was more marked in parenchyma-

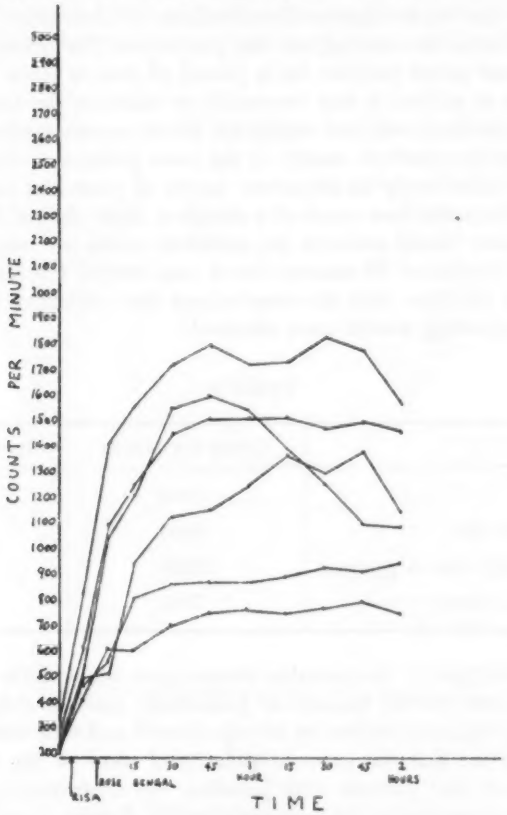

Fig. 3

tous jaundice, while the excretion of the dye appeared to be more delayed in obstructive jaundice. The magnitude of difference was not considered sufficiently impressive to differentiate, for diagnostic purposes, the two types of jaundice. The amount of retention in 9 of the 12 patients with parenchymal jaundice was as great or greater than the retention noted in any of the obstructive jaundice curves. Moreover, the contour of the curve in the cases studied failed to provide

a characteristic pattern which could clearly represent the group of patients with obstructive or parenchymatous jaundice.

Comment

There are many difficulties encountered in employing the radioactive rose bengal test to differentiate the type of jaundice in the patient studied. In attempting to use the test to diagnose hepatocellular or obstructive jaundice, many problems were found in carrying out the procedure. The patient was required to lie in the same prone position for a period of two or more hours, and frequently became so restless it was impossible to maintain the same position. As a result the counterhead and lead collimator would require readjustment, which, of course, was never returned exactly to the same position or degree of angulation. This was undoubtedly an important source of error. An investigation was undertaken to determine how much of a change a slight shift of the counterhead and lead collimator would make on the recorded counts per minute. At 90 minutes after the injection of 30 microcuries of rose bengal the number of counts were taken over the liver with the counterhead and collimator in various positions, and the following results were obtained.

TABLE I

Position	Counts Per Minute	Percentage Change
1. Normal	7093	–
2. 10% toward the feet	8066	12.2
3. 10% toward gallbladder & pancreas	10538	48.5
4. 10% toward the chest	7043	0.7

The gross changes in the recorded counts upon slight shifts of the counterhead and collimator toward the feet or gallbladder make it obligatory that the test be run with rigid supervision by an experienced and well-trained technician. It is firmly believed that the gross irregularity of some of the curves, both in normal individuals and patients with jaundice was contributed to by the restlessness of the subject and inaccurate replacement of the counterhead and collimator. This constitutes an extremely important handicap in carrying out the procedure with consistency and uniformity.

One of the most significant disadvantages of the test is the inability to produce sufficiently definitive or uniformly close end points in the many criteria used for analysis and comparison, such as: 1. maximum peak of the curve, 2. time required to reach the maximum peak, 3. height of the curve at each 15-minute interval following the injection of rose bengal, 4. contour of the curve,

and 5. time required for the curve to return to the level which had been reached three minutes after the injection of rose bengal in patients with jaundice.

The curves showed a high degree of variability in the maximum peak of the curve, the time to reach the maximum peak, and the height of the curve at each 15-minute interval following the injection of rose bengal. This range of variability was found in cases representing normal individuals as well as in those groups of curves obtained from patients with jaundice. Several criteria, however, were recognized to be characteristic of a normal state which were not found in

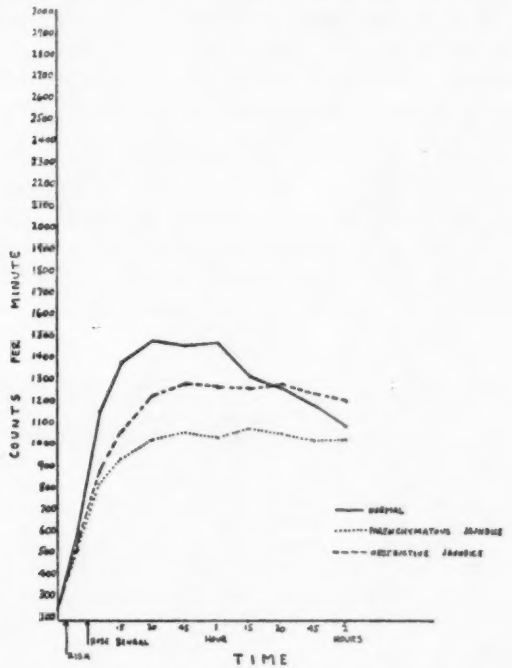

Fig. 4

cases of jaundice. A patient without evidence of liver disease could be distinguished from a patient with jaundice, for example, by determining whether the number of counts after two hours was above or below the level reached three minutes after the dye was injected. In cases of jaundice, a lack of uniformity of the various established criteria again presented difficulties in deciding upon a diagnosis with reasonable assurance of hepatocellular or obstructive jaundice. Although a composite representation of the curves obtained from patients with parenchymatous jaundice could be recognized as differing from a similar composite curve derived from cases of obstructive jaundice, the degree of difference

was not pronounced. In examining the individual curve studies, one finds gross variations in each group with resulting overlap of curves in cases of both types of jaundice. The identity of each type of jaundice therefore tends to be lost, and the reliability of the test is impaired.

Summary

Eighteen normal patients, 12 patients with hepatocellular jaundice, and 6 patients with obstructive jaundice were given an intravenous injection of radioactive rose bengal, a dye known to be selectively taken up from the circulation and excreted by the liver. The amount of radioactivity over the liver was measured at 15-minute intervals for a two-hour period and curves were constructed. The curves showed a high degree of variability in the maximum peak of the curve, the time required to reach the maximum peak, and the height of the curve at each 15-minute interval following the injection of rose bengal in both normal and jaundiced patients. The two-hour end point of the dye in normal individuals returned to the level reached three minutes after its injection. This varied from the result found in jaundiced patients whose curve showed retention of the dye, but the patterns were not sufficiently consistent nor definitive for parenchymatous vs. obstructive jaundice and as a result the test was considered unreliable in differentiating the types of jaundice.

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AN INTERESTING CASE OF HEMORRHAGIC GASTRITIS

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A number of articles have appeared in the recent literature[1-4] on the control of capillary bleeding by the use of adrenochrome. This is a report on an interesting case where large volumes of transfused blood failed to show any demonstrable effects on massive upper gastrointestinal bleeding, and in which adrenochrome displayed rapid action.

Case history:—A 79-year old white female was admitted for vomiting blood. She had done so for a few hours previously, but she had no history of prior episodes or of tarry stools. She had experienced indigestion over the past six months and had become somewhat constipated. Other than being diabetic, which was routinely controlled with diet and 25 units PZI daily, she had no other pathological symptoms.

Positive physical findings:—The patient was pale and comatose with pulse of 125, blood pressure 105/70, respiration 36 and tarry stool on digital examination.

Laboratory data:—Urinalysis showed: specific gravity, 1.014; albumin, 0; sugar, 0; acetone, 0. Blood count: R.B.C., 4.1; Hgb., 80 per cent; hematocrit, 38 per cent; W.B.C., 4,500; polys, 78; lymph, 16. Blood sugar was 303; N.P.N., 68; CO_2, 20 meg.; thymol turbidity, 5 units.

PROGRESS NOTES

The patient was admitted with massive upper gastrointestinal bleeding. She continued to bleed in the hospital as evidenced by the hematocrit dropping from 38 on admission to 35, eight hours after admission. She received transfusions and her hematocrit continued to fall to 33 despite this. A laparotomy and gastrostomy were performed and the patient had a diffuse acute hemorrhagic gastritis. Topical thrombin was sprayed on the gastric mucosa during the operation.

Postoperatively on 21 July, the patient received tropical thrombin by Levin tube and later by mouth every half-hour. In spite of continuous transfusions, her hematocrit, following surgery, dropped as follows:

She was operated on 19 July and given 1,500 c.c. of whole blood. Her hematocrit was 37 two hours following surgery and eight hours following surgery, it was 31.

On 20 July, she was given 500 c.c. of whole blood. At 9:00 A.M., her hematocrit was 36 and at 3:00 P.M., it was 33.

The patient was given 500 c.c. of whole blood at 7.00 A.M. on 21 July, and at 8:00 A.M., the hematocrit was 29.

At this point, it was obvious that the patient was still bleeding. Adrenosem was started at 10:00 A.M., with 1 ampul (5 mg.) being given every two hours for four doses. At 6:00 P.M., she was given 500 c.c. of whole blood and at 9:00 P.M., her hematocrit was 40.

On 22 July, it was 41 and on 25 July, it had gone to 44.

The patient was put on antacids and Sippy regime. She was discharged on 8 August 1956 as recovered.

Figure 1 graphically illustrates the hematocrit course on the patient. This covers the entire five-day period in which she was checked.

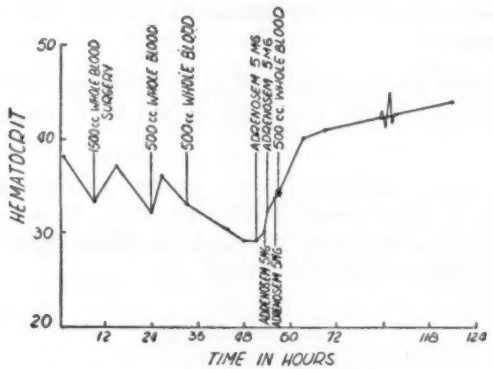

Fig. 1

Conclusion

A patient is presented in which massive bleeding was not controlled by surgery and topical thrombin. This is indicated by a continued decline in the hematocrit reading. Adrenosem® Salicylate* brought about an immediate reversal of this situation. There was no tendency toward bleeding after the Adrenosem therapy was withdrawn.

Summary

1. A case of massive upper gastrointestinal bleeding is presented.

2. Surgery and transfusions were performed.

*Adrenosem® Salicylate supplied by The S. E. Massengill Company, Bristol, Tenn.

3. Bleeding ceased and hematocrit rose consistently after administering Adrenosem® Salicylate.

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THE SURGICAL TREATMENT OF THE TYPHOID CARRIER*

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Typhoid fever is uncommon in the current era. Many medical students and young physicians have never seen a case. Modern methods of food handling, refrigeration, prophylactic inoculation, sanitation, and the unrelenting efforts of our public health departments have all but eradicated this disease.

Most outbreaks of typhoid fever have been traced to individual carriers who periodically discharge typhoid bacilli in the feces. The classic typhoid carrier lived in New York and was Mary Mullen, a cook, who became known as Typhoid Mary. She infected a large number of persons as she moved from job to job in New York City, during the first decade of this century. Recently, Hiddlestone and Murphy reported from New Zealand the history of a woman who lived a nomad existence and preferred the company of goats and dogs to human beings[1]. Her livelihood was derived from selling goats' milk. This woman had been a typhoid carrier for approximately 52 years, during which period she caused several deaths and outbreaks of typhoid fever. She transmitted the disease by the goats' milk.

Eberthella typhosa produces an acute, generalized infection characterized by vague prodromal symptoms, followed by a continued high fever with a relatively slow pulse, rose-colored spots over the abdomen, prostration, abdominal pain and tenderness, splenomegaly, and leukopenia. The peak incidence occurs in the autumn. Sometimes a secondary peak may occur in the winter. Most writers agree that 5 to 10 per cent who recover from the disease excrete the *bacillus typhosus* in the urine or feces for months or years and constitute carriers[2]. These people are a constant and serious menace to the health of their neighbors.

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In September 1954, a case of typhoid fever was diagnosed in the State Park Division of the State Hospital. Subsequently, four additional cases from the same two wards of the Women's Division were diagnosed. All patients on these wards and including those who had been admitted to these two wards within two months preceding the estimated onset of the first case were examined. Examination of these 54 females resulted in positive stool cultures in two of the reported cases. These two were thought to be carriers. Collection of specimens in mental patients was a problem. Rectal swabs were found to be more reliable and a more satisfactory method of collecting specimens for stool culture.

Although our group of four cases is small, we feel justified in adding it to the literature. There has been a scarcity of articles on this subject in the past 15 years in this country. We wish to present this material in order to call the reader's attention to this unusual and increasingly rare indication for cholecystectomy.

Case Reports

Case 1:—M. A., No. 61165, a 30-year old colored female was admitted 18 August 1949 with a diagnosis of schizophrenia, hebephrenic type.

The subsequent history was not remarkable until November 1954. She developed the findings of an acute abdomen and was referred to the surgical ward for observation. An intravenous pyelogram at this time was negative, as was a chest film. After three days' observation, the acute episode subsided. On 23 November 1954, a serum agglutination test revealed a positive titer of typhoid H in 1:320 dilution, with a negative paratyphoid B titer. The stool was reported as growing *bacillus typhosus*. On 2 December 1954, a white blood count of 10,150 was recorded and a differential of 38 per cent polymorphonuclears, 54 per cent lymphocytes, 7 per cent eosinophils, and 1 per cent basophils. The hemoglobin was 11 gm. Sedimentation rate at this time was 38 mm. per hour. The hematocrit was 40 per cent. Repeat serum agglutination series revealed a positive finding in dilution of 1:320. On 5 December 1954, the agglutination test was positive for typhoid H in a dilution of 1:640. Another rectal swab on this date grew *bacillus typhosus*. Repeat white counts over the next several months varied from 5,000 to 6,750 with essentially normal differential counts. Over the next four months, rectal swabs were cultured, growing out *E. typhosus* seven times, but on twelve occasions the cultures were negative. Blood and urine cultures failed to grow any typhoid organisms.

On 2 December 1954, a one week course of Chloromycetin®, 250 mg. q.i.d., was inaugurated, after which rectal swabs cultured continued positive for the typhoid organism. A two weeks' course of this drug was begun on 23 December 1954, with the dose increased to 500 mg. q.i.d. The stool cultures remained posi-

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tive after the course of the drug. On 25 February 1955, the plan was changed to give Chloromycetin, 500 mg. q.i.d. for five days, followed by five days off medication, with a repetition of the drug until the stools became negative. For two months this treatment was followed, but in April the stools continued to grow typhoid. Due to failure of cooperation of the patient, duodenal aspiration and culture were not performed. It was decided that cholecystectomy should be performed. This was carried out on 6 July 1955, by one of us (W.M.L.). The pathologist reported chronic catarrhal cholecystitis, with fibrosis and cholelithiasis.

The bacteriology report on the gallbladder specimen from surgery was positive for *E. typhosus*. Fifteen postoperative rectal swabs when cultured failed to grow the organism.

Comment:—Today in the patient with an acute abdominal disease, typhoid fever seldom, if ever, is considered in the differential diagnosis. Frequent observation and examination of this patient while on the surgical ward ruled out an acute surgical disease. The complications of typhoid fever, namely, intestinal perforation and hemorrhage, are of a surgical nature and may require prompt recognition and intervention.

Case 2:—L. J., No. 44252, a 20-year old colored female, was admitted 19 November 1938. Admission diagnosis was schizophrenia, catatonic type. This patient was employed at times as a waitress in the dining room.

Her course was uneventful until 8 December 1954, when a routine rectal swab culture grew *bacillus typhosus*. She was placed in isolation. Agglutination studies, blood culture, and urine culture were all reported negative. From 13 December 1954 to 27 December 1954, she received Chloromycetin, 500 mg. q.i.d. Agglutination study of 31 December 1954 was negative. The stool culture of 3 January 1955 was positive for the typhoid organism. For the next four-month period, the patient received three additional courses of Chloromycetin, and her stool grew out the typhoid organism six additional times. During this period of time there were reported eleven negative stool cultures. The agglutination titer was never reported positive through May 1955.

During this six-month period, the patient's white count varied from 4,000 to 6,500 with a nonremarkable differential white blood count. It was decided that she was probably a typhoid carrier and that cholecystectomy might produce a cure. Operation was performed on 15 June 1955 (by W.M.L.). The pathologist reported chronic cholecystitis and cholelithiasis. The primary culture of the gallbladder grew out a gram negative bacillus in the *Salmonella Eberthella typhosus* class. Further classification revealed a positive serum agglutination Salmonella polyvalent of Salmonella Group D.

Comment:—In retrospect, it is interesting to note that this patient had worked in the hospital dining room as a waitress. All too frequently, people who

are carriers for some unknown reason gravitate toward food handling occupations. As in the first case, we see the association of chronic gallbladder disease and gallstones with the carrier state. Cholelithiasis is uncommon in the Negro race.

Case 3:—W. M., No. 51084, a 25-year old colored female was admitted on 1 June 1943, with a diagnosis of psychosis, with convulsive disorders (epilepsy), and epileptic deterioration.

In the fall of 1954, she was exposed to typhoid fever. Fecal culture of 10 December 1954 grew out *B. typhosus*. The hemogram showed a hemoglobin of 10.5 gm., a white count of 10,950 with 45 per cent polymorphonuclears, 45 per cent lymphocytes, and 10 per cent eosinophils. Sedimentation rate was 21 mm. per hour. The hematocrit was 42 mm. A stool culture on 13 December 1954 showed no growth of the enteric disease group. The serum agglutination series of 13 December 1954 was positive for typhoid H., dilution 1:40, and paratyphoid B. negative. Subsequent agglutination tests were negative. The patient's white blood count over the next six months varied from 7,250 to 11,000 with a consistently high eosinophil count, reaching 49 per cent. Eleven urine cultures failed to grow any *E. typhi*. The typhoid organism was cultured from the stool six times between December 1954 and April 1955. Negative cultures were obtained on seven occasions during the period. Negative cultures were obtained on 15 June 1955, 14 July 1955 but on 13 July 1955 and 20 July 1955, the stools were positive for typhoid organisms.

Throughout this seven-month period, the patient received courses of Chloromycetin repeatedly in the same dosages as the two foregoing cases, but the stool cultures remained positive for the typhoid organism.

Medical consultants classified this patient as a typhoid carrier. She was unable to cooperate for duodenal aspiration and culture. It was decided to perform cholecystectomy. This was done on 17 August 1955 by one of us (W.M.L.). The culture of the gallbladder grew out the paracolon bacillus but no typhoid organisms were reported.

Comment:—The routine screening of all patients exposed to a case of typhoid fever yielded this patient among others as a carrier. Over the 12 years she had been in the hospital she never presented the clinical findings of the acute typhoid state. In view of her preoperative laboratory findings but negative gallbladder culture postoperatively, it would be unreasonable to classify her as anything but a chronic carrier.

Case 4:—No. 643244, a 15-year old colored female was admitted 7 March 1951, as a mental defective (imbecile).

In September 1954 she developed a clinical picture compatible with typhoid fever. On 9 September 1954 her typhoid agglutination titer was positive

in a dilution of 1:320. A week later the titer rose to 1:1280 but slowly decreased until June 1955 at which time it was positive, 1:80 dilution.

This patient's first stool culture to grow *B. typhosus* was on 3 October 1954, the fourth week of the disease. During the following year she had four stools grow *E. typhosus* out of 25 cultures with three of the four positive results occurring in November 1955, more than a year after her typhoid fever.

She was classified as a typhoid carrier. Cholecystectomy was performed on 21 December 1955 (by W.M.L.). During the first month postoperatively, we obtained three positive rectal swab cultures but ten others were negative. Since then 15 stool cultures have been reported negative.

Comment:—Evidently, this patient contracted typhoid fever from one of the above carriers. She failed to clear of typhoid organisms under intensive medical therapy. She represents one of the small percentage of people who remain carriers after acute typhoid fever.

Classification

Typhoid carriers may be classified as convalescent or chronic. A convalescent carrier is one who has recently recovered from the disease and who has a positive urine or stool culture for some six to eight months following infestation. Thereafter, he remains completely free of organisms and is no source of concern. The patient, however, who continues to excrete in the urine or feces, for a year or longer, typhoid organisms is definitely a threat to the welfare of the community and is classified as a chronic typhoid carrier.

It is generally recognized that the human body may harbor the typhoid organism in one of four places: 1. the urinary tract; 2. the intestinal mucosa or Peyer's patches; 3. the biliary radicles of the liver; or 4. the gallbladder. Of the patients who remain carriers, some 75 to 80 per cent harbor the organism in the gallbladder.

Diagnosis

Blood culture is often positive in the first week of the disease. The Widal reaction is positive in at least 90 per cent of the cases after the first seven to ten days. The stool and urine cultures become positive in the second and third weeks of illness. In the Widal reaction, any titer greater than 1:40 should be considered significant. The titer may go as high as 1:20,000 but frequently remains in the hundreds[2]. A patient who has had typhoid fever should be followed for a minimum of a year and should have six to eight negative stool cultures and two or three duodenal drainage cultures, all reported negative, prior to being reported as a cured case.

If upon duodenal intubation the fasting bile should grow out *E. typhosa*, the investigator would assume that the residual infection was in the hepatic

radicles. If after stimulation of the gallbladder the bile so obtained grew a positive culture of *Salmonella typhosa*, the investigator would likewise assume that the patient was a gallbladder carrier. A negative duodenal intubation with positive fecal culture does not rule out biliary tract infection. The collection of the bile for culture and methods employed are of some import. It has been said that the bile specimen must be clear, amber, viscous, and alkaline, must be obtained following stimulation with magnesium sulfate, and must be protected and buffered while on its way to the laboratory. Reliance on cultures with a pH below five is poor, and cultures of infected bile specimens with pH of two or less after 30 seconds yield no growth. Bile and gastric juice change color rapidly and hence this characteristic should be recorded immediately. In general, the color changes from blue-green to green, to yellow, to amber, with decreasing acidity of the mixture. Thus, shades of yellow may be satisfactory and amber usually is for bacteriologic examination[3].

In a financially handicapped institution with uncooperative patients and shortage of personnel, it is evident that such thorough investigation could not be performed in the present series of cases.

Treatment

It is general information that Chloromycetin (chloramphenicol) is the drug of choice in acute typhoid fever. Such is not the case, however, in dealing with the carrier state. The four present cases bear witness to this fact, and the literature is replete with case reports where this drug has failed and where surgery has succeeded in curing the typhoid carrier[4].

When a sufficient period of time has elapsed after the acute disease and the patient continues to have positive stool cultures and/or bile cultures, one should endeavor to have the patient undergo cholecystectomy. This is especially so since the results have been so uniformly successful following this procedure. Obviously, it may be difficult to get a person to submit to cholecystectomy when he is suffering little or none at all from his carrier state. Should the patient refuse, the court may order the patient to submit. In some countries, the health officer may order the patient to undergo hospitalization and treatment as a carrier.

The carrier state, once diagnosed, poses certain difficulties, particularly in a large institution where great numbers of patients live in close proximity. It is needless to point out the danger of a typhoid epidemic in a mental hospital. A carrier detected in a normal environment should be made to understand clearly in what way he is a danger to his neighbors. No carrier should engage in the purveyance or preparation of edible items. This includes all forms of liquids, especially milk. Such patients should be encouraged to accept surgery. If there is a medical contraindication to surgery, the patient all the more should be thoroughly indoctrinated about his condition and educated to be scrupulously

clean in his personal hygiene and in his contacts with other members of society. The typhoid carrier who is not amenable to surgical intervention is subsidized in some states to make him sufficiently independent so that his working would not endanger the lives of his fellows. In this hospital, if the family does not grant permission for operation if it is deemed advisable, or if the family cannot be located to grant permission for the patient in question, application is made to the district court which may order the operation performed to protect the remaining patients.

Results

To date, there is no effective nonsurgical treatment for the carrier state. Since 1907, when Dehler reported the cure of a carrier by cholecystectomy, and the following year Grimme reported a cure, many reports of surgical treatment have appeared. In 102 cases collected in the European literature until 1930 by Eichoff in which cholecystectomy had been employed for the chronic typhoid carrier, he found that 81 per cent were cured by operation[5]. He chose six months postoperatively as a minimum period for evaluation, for it is well known that stools of some carriers do not clear up immediately but may continue to yield positive cultures for some months after surgery. In 1937, Collier and Forsdeck added 18 cases to 55 cases from the literature and reported 76.9 per cent cures. Crabtree, in 1942, added 21 cases to the previous group reported by Collier and found that 88.9 per cent had been cured by cholecystectomy.

Every stool culture taken of our four patients since cholecystectomy has been negative, except Case 4 who had three positive stools the first month postoperatively. There has been a follow-up period of from 12 to 18 months in these cases with a minimum of 15 negative stool cultures per patient. We consider our patients cured, a cure rate of 100 per cent.

Comment

All of our patients were in excellent condition for surgery. Once the medical regime had failed for six months and had been proven a failure by repeated positive rectal swabs, the patients were selected for surgery. No special preoperative preparation was carried out on these individuals. Each of them was an excellent risk, without other mitigating disease. Under G.O.E. anesthesia, operation was performed through a right subcostal incision. Each patient received intravenous fluids throughout the procedure. The surgical principles of adequate hemostasis, good exposure, careful dissection, and anatomic identification of the common duct, cystic duct, hepatic artery, and cystic artery were carried out. In two cases, the cystic artery and cystic duct were ligated and the gallbladder was removed in the retrograde fashion, adhering to the well founded principles of surgery in this area. In the other cases, the organ was removed from above downward. A drain was inserted in each case and removed

on the fifth day. Each patient received penicillin and streptomycin for seven days postoperatively. No complications were encountered in this series of cases.

In Case 3, we are at a loss to explain why the gallbladder as removed at operation did not yield a positive culture. This patient's stools have likewise remained negative. It may be explained on the basis of a technical error on the part of the laboratory personnel, or it may be that this patient spontaneously discontinued excreting typhoid bacilli in her stool.

In reviewing the literature, we did not encounter a report of an operative fatality for this situation. This is an important point to keep in mind when one is dealing with a carrier and attempting to convince the patient to undergo cholecystectomy, especially when he is free of symptoms and one is discussing operation with him. Although the surgeon cannot guarantee a cure to the patient, the results speak for themselves. This is unquestionably the most reliable method of dealing with the problem. In addition, these patients have a much higher incidence of cholelithiasis and cholecystitis than the population at large. Usually one can help the patient benefit his general physical well-being by performing cholecystectomy upon him and at the same time bestowing a blessing to the health and welfare of his fellow citizens.

Summary and Conclusions

1. Cholecystectomy was performed upon four mental patients who were diagnosed as chronic typhoid carriers.

2. The four patients are considered as cured.

3. In the chronic typhoid carrier state, cholecystectomy offers the single most successful method of dealing with the typhoid carrier for which there is no nonsurgical treatment.

Acknowledgment

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THE MILK-ALKALI (BURNETT'S) SYNDROME

Two Case Reports

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This presentation is made: 1. to report two additional cases of a condition that is rare in the sense that the disease has been described relatively recently and only a few well documented cases have been recorded; 2. to stimulate clinical awareness of the presence of this entity since we feel it occurs more frequently than statistics would have us believe; 3. since the process is reversible, if recognized early, reversal of renal failure may be effected.

In 1949, Burnett and co-workers[2] first described a very interesting clinical syndrome of metastatic calcification after a prolonged and excessive intake of milk and alkalis in ulcer patients. They reported six clinical cases with this syndrome and found that these patients had metastatic calcification without primary hyperparathyroidism; i.e., hypercalcemia, no hypophosphatemia, and no hypercalcinuria, with or without alkalosis. If therapy was not initiated for these patients, they usually terminated with renal insufficiency secondary to nephrocalcinosis. They also found that metastatic calcification usually occurred in organs such as the kidney, stomach, and lungs which excrete acids while the tissues themselves remain alkaline.

Before Burnett's first description of this syndrome[2], however, an entity of metastatic calcifications of the various organs and causes had been described by many investigators since Virchow in 1895. Experimental work on animals and clinical complications due to metabolic alkalosis by alkali administration were also reported by authors such as Butler[3], Hardt[9], Jeghers[11], Cooke[5,6], Kirsner[12], Grace[10], and others.

After Burnett's report in 1951[2], Becker and his associates reviewed 99 autopsied cases with duodenal ulcer and found a high incidence (36 per cent) of renal parenchymal calcinosis[1]. They stated that 68 per cent of these patients had a history of high intake of alkali and/or milk, but did not necessarily have the clinical symptoms before death.

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In 1953, Werner reported one case with this syndrome[19], and in 1954, Dufault reported four similar cases[7]. These investigators found that this type of metastatic calcification was reversible with a proper diet and a regime omitting alkali and milk intake.

In 1954, Snapper reported two additional cases[18], and in 1955, Schneider reported one case[17]. These authors discussed the pathogenesis and clinical features in detail, and also the differential diagnosis of this syndrome from hyperparathyroidism with renal insufficiency[4,13].

Recently, we observed two similar cases at the Jersey City Medical Center. One patient was slightly improved clinically with conservative therapy, and the other expired shortly after because of uremia.

Case Reports

Case 1:—H. D., J.C.M.C. #177039. A 42-year old white male clerk was first admitted to the Jersey City Medical Center on 7 March 1956 with one week's history of progressive mental clouding. During his military service in 1942, he had severe jaundice and also a duodenal ulcer. He was advised at that time to take milk and sodium bicarbonate whenever he had epigastric pain. Since then, he drank four or five quarts of milk and ingested large amounts of sodium bicarbonate daily. He had consumed large quantities of beer and whiskey for for several years. His appetite had been poor for more than ten years. Following his drinking episodes, he experienced epigastric pain, nausea, and vomiting. About three weeks prior to admission, he began to feel weak and ill. One week before hospitalization, he gradually became drowsy and weaker and was confined to bed without food. He had vague epigastric pain, nausea, vomiting, and marked malaise.

Physical examination on admission revealed a well-developed, well-nourished, obese white male who looked acutely and chronically ill with semiconsciousness, dehydration, and Kussmaul breathing. Blood pressure was 135/80, pulse 104, temperature 98, and respiration 35. Head, eyes, ears, nose and throat were essentially negative except for the fundoscopy which revealed arteriolar spasm without hemorrhage. The tongue was very dry and coated. Heart was within normal limits. The diameter of the chest was increased posteroanteriorly. Breath sounds were diminished. No rales were audible. The abdomen was very adipose and no masses or tenderness were noted. There was increased venous collateral circulation on the surface. The liver was not palpable. There was no evidence of peripheral edema. No skin nodules or *spider nevi* were noted.

Laboratory findings:—Urinalysis showed amber color, specific gravity 1.016, acid, albumin 1 plus, sugar 4 plus, acetone 1 plus, diacetic acid negative, white blood cells 8-10 per high power field. Red blood count 5.19 million, white

TABLE I

CLINICAL FEATURES

No.	Authors	Age	Sex	Location of Ulcer	Duration (Years)	Milk (Qts. Daily)	Alkali	Course
1	Burnett	44	M	Gastric	33	Several	$NaHCO_3$	Expired *
2	Burnett	25	M	Peptic	3	Large Amount	$NaHCO_3$	Expired
3	Burnett	44	M	Duodenal	25	Large Amount	$NaHCO_3$	Improved
4	Burnett	38	M	Duodenal	12	3	$NaHCO_3$	Expired
5	Burnett	55	M	Peptic	18	5	$NaHCO_3$	Expired
6	Burnett	54	M	Duodenal	30	Several	$NaHCO_3$	Improved
7	Miller	41	M	Duodenal	9	5 Glasses	$NaHCO_3$	Improved
8	McQueen	67	M	Duodenal	6	4	Alkali Powders	Improved
9	Mulholland	37	M	Pylorospasm	30 ?	2	Tums †	Improved
10	Mulholland	41	M	Duodenal	14	2	Bismadine ‡	Improved
11	Werner	67	M	Duodenal	13	3	$NaHCO_3$	Expired *
12	Dufault	57	M	Duodenal	25	1	$CaCO_3$	Improved
13	Dufault	52	M	Duodenal	28	3	$NaHCO_3$	Improved
14	Dufault	52	M	+	35	2	$NaHCO_3$	Expired *
15	Dufault	50	M	Duodenal	20	4	$CaCO_3$ $NaHCO_3$	Improved
16	Snapper	62	M	Peptic	10	3	Alka-Seltzer	Improved
17	Snapper	65	F	Peptic	11	None	Alka-Seltzer	Improved
18	Dworetzky	50	M	Duodenal	28	8	$NaHCO_3$ $CaCO_3$	Improved
19	Kyle	49	M	Duodenal	25	3	$NaHCO_3$	Expired *
20	Schneider	63	M	+	5-1-?	Large Amount	Tums ‡	Improved
21	Case 1	42	M	Duodenal	22	5	$NaHCO_3$	Expired *
22	Case 2	53	M	Duodenal	20	4	$NaHCO_3$	Improved

+ Not noted in literature
* Autopsy performed

† Calcium Carbonate, Magnesium Carbonate, Magnesium Silicate, Peppermint
‡ Bismuth Subcarbonate, $NaHCO_3$, Calcium Carbonate, Magnesium Hydroxide, Diastase, Oil of Peppermint

blood count 14,600, hemoglobin 15.3 gm.; differential: bands 2, filament 69, lymphocytes 28, monocytes 1. NPN ranged from 135 to 157 mg. per cent; blood sugar ranged from 360 to 510 mg. per cent; CO_2 33.0 volumes per cent; creatinine 6.05 mg. per cent; inorganic phosphate 4.6 mg. per cent. Sulkowitch test was very faintly positive.

An electrocardiogram revealed a sinus tachycardia and prolongation of QT interval. A chest x-ray was within normal limits (J.C.M.C. #56-5210).

Hospital course:—Shortly after admission, the patient went into a deep coma and could not be aroused by painful stimuli. Hyperglycemia and glycosuria were discovered although no previous history of diabetes was obtainable. The accepted measures for the treatment of diabetic acidosis and renal insufficiency were immediately instituted. In spite of all efforts, however, the pattern

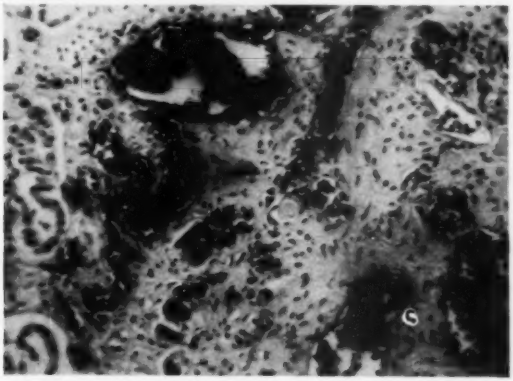

Fig. 1—Kidney showing calcification of the parenchyma and the tubules.

of renal failure progressed and the patient expired 36 hours after admission without regaining consciousness.

Autopsy report:—(J.C.M.C. #6588). The body is that of a 42-year old white male, well-developed and very obese, measuring 75 inches in length. There was 3 plus rigor mortis and 1 plus postmortem lividity. There was no edema. The skin was clear. There were no lymph nodes. Eyes, ears, nose and throat were negative. The pupils measured 3 mm. There were no external marks.

An incision extending from the xyphoid process down to the pubis was made. The abdominal cavity was free of fluid. The organs were normal in position and relation. The peritoneal surfaces were smooth and glistening. There was an excessive amount of fat in the omentum and mesentery. The spleen weighed 350 gm. The surfaces were smooth and slate colored. On cut section, the surfaces were homogenous and dark red.

The cardioesophageal junction appeared to be normal. The stomach was distended and contained a dark brownish material. There was an active penetrating ulcer at the first portion of the duodenum measuring 1.5 cm. in diameter. The pancreas weighed 200 gm. and presented the same described area of penetration with an inflammatory reaction. The liver weighed 5,300 gm. It had a yellow, greasy tinged appearance. On cut section, there was chronic passive congestion with a nutmeg appearance. The gallbladder wall was thickened and the mucosa was greenish in color and did not contain stones. Each kidney weighed 250 gm. The external surface was irregular with cystic areas containing

TABLE II

Symptomatology (20 cases)	No. of Cases	Percentage
Epigastric Pain	17	85
Weakness and Fatigue	13	65
Polyuria and Nocturia	12	60
Pruritus	10	50
Nausea and Vomiting	10	50
Weight Loss	8	40
Joint Pains	7	35
Nervousness	6	30
Polydipsia	5	25
Anorexia	4	20
Insomnia	4	20
Dryness of Skin	3	15
Heartburn	2	10
Vision Disturbance	2	10
Muscle Ache	2	10

clear yellowish fluid. The capsule stripped with some difficulty. The medulla measured 2 cm. and the cortex 0.1 cm. There were small areas of dark reddish discoloration at the cortex. No calcifications were seen macroscopically. The left pelvis and ureter were thickened and contained a moderate amount of urine and pus. The right adrenal weighed 15 gm. and had a normal appearance. The left adrenal weighed 25 gm. The cortex was of average thickness and color. The medulla was dilated and filled with fresh blood. Areas of clotted blood were also seen. The wall of the urinary bladder was thickened. The mucosa was hemorrhagic and contained purulent material. All external genitalia were normal. The prostate was not enlarged.

Microscopical description:—The duodenum showed margins of orderly mucosa and a central deep ulcer which had superficial necrosis with polycystic infiltration and a base of fibrous tissue containing arteries and veins. The scanty periportal tissue of the liver was infiltrated with lymphocytes. Almost all of the liver cells contained very large, clear vacuoles. The spleen and pancreas sections were histologically normal. In each kidney, many tubules were filled with basophilic calcification (Fig. 1); in some of these areas, the tubules were destroyed and the calcified masses were surrounded by lymphocytes. There was

Fig. 2—Right shoulder x-ray showing a large calcification adjacent to the greater tuberosity of the humerus.

focal interstitial lymphocytic infiltration. The adrenal sections were histologically normal. The pathological diagnosis was: duodenal ulcer; nephrocalcinosis; pyelonephritis and fatty liver, severe.

Case 2:—M. T., J.C.M.C. #097642. A 53-year old white male clerk was first admitted to the Jersey City Medical Center 1 October 1953 because of subcutaneous masses over the right wrist and both anterior chest walls. The patient disclosed a 20-year history of duodenal ulcer which was confirmed by a previous gastrointestinal series.

He had intermittent epigastric pain which was relieved by milk or soda bicarbonate. He had consumed two to three quarts of milk daily for the past three years and ingested one to two tablespoonsful of soda bicarbonate daily for one year.

The diagnosis of diabetes mellitus was made in 1949 and the patient was put on therapy of 17 units of NPH insulin daily without any dietary restrictions. Two months prior to admission, he noticed nodules over the right wrist and both anterior chest walls which became progressively larger. He also experienced fatigue, weakness, frequent urination, nocturia, and pruritus.

Systemic review disclosed intermittent unproductive cough for ten years and occasional ankle edema for the past six years. The patient smoked two packs of cigarettes daily and drank an occasional highball. Family history revealed that one brother had died of carcinoma of the stomach.

Physical examination revealed a well-developed, well-nourished male who looked pale. Eyes, ears, nose and throat were negative. The chest showed an increased diameter posteroanteriorly. There were two nontender subcutaneous masses on both anterior chest walls adjacent to the inferior distal clavicular region. The left mass measured 4 x 6 cm., and the right mass 15 x 10 cm. The lungs and heart were essentially negative, but a soft apical systolic murmur was heard. The abdomen was negative.

There was a nontender subcutaneous mass over the ulnar aspect of the right wrist measuring 4 x 4 cm. Subcutaneous masses were also present on the left and right elbows measuring 8 x 4 cm. and 4 x 4 cm. respectively. The skin was pale and the turgor was markedly decreased.

Laboratory findings:—Urinalysis showed specific gravity 1.015, albumin 2 plus, sugar negative, occasional red blood cells and white blood cells. Fishberg concentration showed hyposthenuria in each specimen. Sulkowich test was positive for small quantities of calcium. Red blood count was 1.99 million, hemoglobin 5.5 gm., hematocrit 31 per cent, white blood count 8,800. NPN was 158 to 137 mg. per cent; CO_2 combining power 18.0 m.E.q.; uric acid 4.8 mg.; creatinine 7.2 mg.; calcium 7.6 to 9.4 mg.; phosphorus 10.0 to 5.8 mg.; potassium 3.94 m.E.q.; sodium 136.8 m.E.q.; alkaline phosphatase 4.0 Podansky units; blood sugar 100 to 131 mg. per cent; total protein 5.5 gm.; albumin 3.7 gm.; globulin 1.8 gm.; cholesterol 188 mg.; esters 59 mg.; cephalin flocculation negative; thymol turbidity .5 units. Serology was negative. Basal metabolism rate was plus 38.

An electrocardiogram showed left ventricular hypertrophy with myocardial ischemia. Right wrist x-ray revealed irregular calcification in the anterior and medial aspects of the wrist measuring 3 cm. in diameter (Fig. 2). Right shoulder x-ray revealed a large calcification just adjacent to the greater tuberosity of the humerus (Fig. 3). In addition, there was a large amorphous calcification

TABLE III

LABORATORY FINDINGS

No.	NPN (mg. %)	CO_2 (m.E.q./L)	Ca (mg. %)	P (mg. %)	Alkaline Phosphatase (B. U.)	Protein (gm. %)	Alb. (gm. %)	Glob. (gm. %)	Albumin Urine	Ca Urine
1	58-80-150	27.4	12-16.6-7.7	4.0-9.4	1.7-18.0	9.2-7.8	6.6-3.6	5.1-2.7	+++	87 mg.
2	85-40	23.3-34.2	12-12.8-11.2	*	2.8-6.8	7.1	*	*	+++	Absent
3	198-90-64	30-35	12.4-12.8-10.6	5.6-2.0	7.2-3.4	7.7	4.6-2.1		++	109 mg.
4	78-64-160	26.8-20.0	12.5-13.5-6.0	6.5-6.4	*	6.5-5.6	*	*	*	*
5	89-90-137	32	11-14-12.8	4.1-5.4	3.2-5.4	7.6-7.2	4.7-2.9		+++	77.8 mg.
6	131-82-62	33-29	11.5-10.9	4.6-1.5	4.4-3.66	4.6	3.6-1.0		*	*
7	232-46.5	35-20	9.2-11.5-10	4.8-4.0	4.8	*	*	*	Trace	*
8	138-125-137	39-29.5	12-13.4	3.9-3.5	12-8 (K.A.)	*	*	*	+	*
9	BUN 136 72	27-29.7	14.4-10.7	4.0-3.3	2.2	7.3	*	*	Trace	16 mg.
10	BUN 107 48	29.7 18	13.0-9.8	5.1-2.9	6.8	7.8	2.0-1.0		+	80 mg.
11	BUN 40-62	6.4-17.2	10.8-11.8	3-5	3-5	7.2	4.9-2.3		Trace	Normal
12	BUN 51-41-14	24-31	12.8-10.1	3.4-4.0	2.6-1.2	*	*	*	++	Normal
13	BUN 60-53-29	40-29	16.0-10.0	4.2-3.2	1.6-3.0	*	*	*	+	Normal
14	BUN 66-78-170	30-16	14.5-9.3	5.6-10.6	4.0-1.0	*	*	*	+	Normal
15	BUN 54-68-59	37-32	11.5-10.5	6.0-4.0	2.0-2.0	*	*	*	+	Normal
16	BUN 53	15	9.3	*	12 (K.A.)	5.0	2.7-2.9		*	Normal
17	31.7-43.4-54.5	*	10.3-11.5	5.5-6.4	12 (K.A.)	6.2-5.2	4.5-1.7		*	Normal
18	BUN 138-125-137	23-20	9.0-9.9	3.5-4.6	4.5-5.2	6.8	4.8-2.0		+	+
19	132-42-38	32-26	12.1-10.8	11.4-5.0	4.9-6.5	6.4	4.3-2.1		++++	110-262
20	42-59	32-43	14.2-15.0	3.3-5.1	*	*	4.3-3.3		+	36-165
21	135-157	15.5-15	*	4.6	*	*	*	*	+	Normal
22	158-118-85	33	7.6-9.6	10-11.3	3.4	5.5	3.7-1.8		+	Normal

*Not reported in the literature

within the projection of the shoulder joint extending mesially measuring approximately 10 cm. in its long axis. X-ray of the lung fields revealed considerably increased markings at both bases especially on the right. X-ray of the abdomen showed the presence of minute calcifications to the right of the superior margin of L_4. Gastrointestinal series showed a deformed duodenal cap with a suggestive crater. At six hours, there was a slight residue in the stomach and duodenal bulb. Gallbladder series and skull x-ray were negative.

Hospital course:—The patient was treated conservatively with an ulcer regime (milk and alkali being omitted). His diabetes was controlled without insulin. He improved subjectively and was discharged 25 October 1953.

He was re-admitted to the Jersey City Medical Center 6 December 1953 with a history of vomiting, epigastric pain and weakness. The physical examination was the same as on the previous admission.

Laboratory findings:—Urinalysis straw, cloudy, specific gravity 1.005, albumin 2 plus, sugar negative, white blood cells few. Red blood count 3.81 million, white blood count 16,950. NPN was 118 to 85 mg. per cent; blood sugar 100 mg. per cent; calcium 9.6 mg.; phosphorus 12.2 mg.; potassium 4.3 m.E.q.; chlorides 85.9 m.E.q.; creatinine 4.8 mg.; and CO_2 combining power 15.5 m.E.q. The patient was treated with blood transfusions and discharged 24 December 1953.

He was re-hospitalized in the Jersey City Medical Center 13 February 1954 with two days' history of epigastric pain and vomiting. The physical examination and laboratory findings were the same as on previous admissions. He was treated conservatively as before and was discharged 23 February 1954. He has not been seen in this hospital since that time.

Patient subsequently expired at home; autopsy was not performed.

Comment

These cases appear to have clinical features and laboratory findings similar to those described by Burnett in 1949. The first patient was hospitalized with severe renal failure, mild diabetic acidosis, decompensated portal cirrhosis, and active duodenal ulcer. On admission, diabetes was discovered and treated with an intensive diabetic therapy including frequent urine tests, insulin and fluid administration. Shortly after admission, however, the patient expired because of the foregoing complications. The diagnosis of Burnett's Syndrome was made but death came before further management of this syndrome could be effected. Chelating agents had been tried with equivocal results—possibly due to the existence of irreversible renal failure at the time of recognition.

The second case was observed for a fairly long period. This patient had massive subcutaneous calcium deposits, renal insufficiency, and mild diabetes

mellitus. After cessation of alkali and milk intake, the patient had clinical improvement and the NPN was markedly decreased.

It is an interesting fact that both of these cases were associated with diabetes mellitus, the significance of which is not clear at present.

We reviewed the clinical features, laboratory and pathological findings of 22 previously reported cases including the two recorded in this paper (Tables I, II, III and IV). Most of the patients were of the middle or slightly older age

Fig. 3—Right wrist x-ray showing calification in the anterior and medial aspects.

groups, average age 51 years. All but one of the patients reported were males. This fact is probably due to the higher incidence of peptic ulcer in males in the United States. The location of the ulcer was chiefly in the duodenum. As is well known, the patients with duodenal ulcer have a higher gastric acidity and more symptomatology such as epigastric pain and vomiting than the patients with gastric ulcer alone.

Each patient had a long-standing history of excessive milk and alkali ingestion (sodium bicarbonate, calcium carbonate, Alka-Seltzer, Tums, and others) (Table I). H. D. (Case 1) of our study was accustomed to taking

TABLE IV

PATHOLOGICAL FINDINGS

No.	Distribution of Metastatic Calcifications						Parathyroid Gland	Kidney
	Kidney	Subcutaneous	Lung	Vessels	Eye	Others		
1	+	+	°	+	+	Diaphragm, Dura Mater, Tendon	Normal	Chronic Pyelonephritis
2	°	+	+	°	+	*Dura Mater, Falx Cerebri*	°	°
3	°	−	°	+	+		°	°
4	°	−	°	°	+		Secondary Hyperplasia	°
5	°	+	°	°	+		°	°
6	°	−	°	°	+	Lymph node	°	°
7	°	°	+	°	+	Lymph node	°	°
8	°	+	°	°	+		°	Normal
9	°	°	−	−	+		°	°
10	°	°	°	°	+		°	°
11	+	+	+	+	−		Secondary Hyperplasia	Glomerulonephritis
12	°	°	°	°	°	Ureterlithiasis	°	°
13	°	°	°	°	+		°	°
14	+	+	+	−	−	*Falx Cerebri*	Secondary Hyperplasia	Pyelonephritis
15	+	+	°	°	+		°	°
16	°	+	+	+	−		°	°
17	°	+	−	+	+		°	°
18	+	+	−	+	+	Urinary Calculi, Skull	°	Pyelonephritis Hydronephrosis
19	+	−	+	+	+	Liver, *Dura Mater,* Adrenal	°	Horse Shoe Hydronephrosis, Pyelonephritis
20	+	°	°	°	−		Normal	°
21	+	−	−	+	−		Normal	Pyelonephritis
22	°	+	+	+	−	Lymph node	°	°

°Not reported in the literature

sodium bircarbonate, "like eating candy". All the patients had epigastric pain or heartburn as the symptoms of ulcer and, therefore, consumed large amounts of alkali and milk for relief of this disturbance.

Later on, these patients began to have pollakiuria, nocturia, polyuria, polydipsia, weakness, fatigue, weight loss, pruritus, dry skin, joint pain, body ache, nausea, and vomiting (Table II). These symptoms were probably due to hypercalcemia, renal insufficiency (nephrocalcinosis), and sometimes due to the peptic ulcer itself.

The laboratory findings (Table III) revealed albuminuria, hyposthenuria, normal excretion of urinary calcium, occasional microscopic hematuria, pyuria, and cylindruria. Most of the patients had consistent azotemia, hypercalcemia (occasional normal serum calcium), hyperphosphatemia, normal alkaline phosphatase, variable total protein, and low or high CO_2 combining power. The patients first began to have metabolic alkalosis due to alkaline ingestion and occasional vomiting as a symptom of peptic ulcer, but as nephrocalcinosis with renal insufficiency advanced, they developed metabolic acidosis because of retention of acid radicles such as sulfates and phosphates. The improvement of this syndrome was accompanied by falling of the NPN and serum phosphate level, and vice versa.

From the pathological findings reviewed (Table IV), it was difficult to evaluate the exact distribution of metastatic calcification as only five of the reported cases were autopsied[2,9,13,19]. Clinically, calcium deposits were found mainly in the subcutaneous tissues, cornea, and conjunctiva. The x-ray films demonstrated pulmonary calcinosis, nephrocalcinosis, vessel calcifications, but rarely central nervous system calcifications *(dura mater* and *falx cerebri)*. The autopsied cases revealed nephrocalcinosis and other kidney pathology, mainly chronic pyelonephritis. It was previously stated that nephrocalcinosis was not due to primary kidney disease[2,18], but we could assume that kidney inflammation might precipitate calcium deposition as a basis of dystrophic calcification in the affected area. Of course, the primary mechanism of metastatic calcification in this entity as previously described, is secondary to the fact that the organs such as the stomach, kidney, and lungs excrete acid but the tissues themselves remain alkaline. Furthermore, alkalosis which was caused by alkali ingestion precipitates calcium deposition in the above mentioned organs. Other areas of rare metastatic calcification were noted in the diaphragm, lymph nodes, tendons, muscles, liver and adrenals.

Of 7 parathyroid glands examined by biopsy and at autopsy, 3 showed secondary hyperplasia due to renal insufficiency, 3 were normal, and 1 was not identified[2,6,13,17,19].

Carpenter[4], Kyle[13], and Schneider[17] reported that patients with clinical features, pathological and laboratory findings similar to Burnett's syndrome were found by biopsy to have primary hyperparathyroidism (adenoma of para-

thyroids). Therefore, it is important to explore the parathyroid gland in order to differentiate Burnett's syndrome from primary hyperparathyroidism.

Summary

Two cases of metastatic calcification secondary to prolonged milk and alkali intake (milk-alkali syndrome) were described and discussed. Twenty-two previously reported cases including the two recorded at this hospital were reviewed and summarized from the viewpoint of clinical features, laboratory and pathological findings.

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HEXOCYCLIUM METHOSULFATE, A NEW ANTICHOLINERGIC: SOME CLINICAL IMPRESSIONS

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Despite the large number of anticholinergic drugs which have been made available through pharmacological research, the need continues for one which is free from unwanted side-effects. It must be admitted, however, that the ideal anticholinergic is unlikely ever to be discovered, since any drug which inhibits cholinergic innervation in one part of the body is almost certain to inhibit it to some extent in another.

Nevertheless, as the search for better anticholinergics has progressed, it has been found possible to develop newer ones with actions more specific than those of older drugs[1,2]. One such newer anticholinergic is hexocyclium methosulfate, which is marketed under the trade-name Tral†.

Naturally there is always hope that the latest anticholinergic will prove to exhibit worthwhile advantages over its predecessors, particularly in regard to specificity. It was for this reason that the present study of hexocyclium methosulfate was undertaken.

Procedure and Results

This study is concerned with 60 cases of various gastrointestinal conditions, including 26 cases of duodenal ulcer, 28 cases of irritable colon, and 6 cases of other such conditions. The patients were all between 20 and 70 years of age, with slightly more than half between 30 and 50. There were 29 men and 31 women.

All patients were given anticholinergic medication 4 times a day, namely before meals and at bedtime. Treatment with hexocyclium (i. e., hexocyclium methosulfate) continued for more than 56 days in 14 cases, 42 days in 8 cases, 28 days in 28 cases, and 14 days in 10 cases. Some patients received concurrent antacid therapy.

The accompanying table summarizes the dosages employed and the results obtained. The results were rated as "excellent" when relief from symptoms was prompt and complete, and side-effects presented no problems; "good" when relief was marked, but slightly less than complete; and "fair" when relief was appreciable, but not sufficient to be wholly satisfactory.

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†Tral (Hexocyclium Methosulfate, Abbott) for the present clinical investigation was supplied by the manufacturer, Abbott Laboratories, North Chicago, Ill.

TABLE I

CASES OF GASTROINTESTINAL CONDITIONS UNDER TREATMENT, DOSAGES OF HEXOCYCLIUM AND PHENOBARBITAL, AND QUALITATIVE RESULTS

Diagnosis	Dosage q.i.d.	Cases	Results			
			Excellent	Good	Fair	*
Duodenal Ulcer	Hexocyclium 25 mg.	15	9	3	3	—
	Hexocyclium 25 mg. Phenobarbital 15 mg.	5	4	—	1	—
	Hexocyclium 12.5 mg.	4	1	2	1	—
	Hexocyclium 12.5 mg. Phenobarbital 15 mg.	2	1	1	—	—
Irritable Colon	Hexocyclium 25 mg.	8	5	3	—	—
	Hexocyclium 25 mg. Phenobarbital 15 mg.	10	4	4	2	—
	Hexocyclium 12.5 mg.	4	2	2	—	—
	Hexocyclium 12.5 mg. Phenobarbital 15 mg.	6	1	4	—	1
Hiatus Hernia	Hexocyclium 25 mg.	1	—	—	1	—
Ulcerative Colitis		2	1	1	—	—
Ileitis		1	—	1	—	—
Diverticulitis	Hexocyclium 25 mg.	1	—	—	1	—
Hyperacidity	Phenobarbital 15 mg.	1	1	—	—	—
Totals	—	60	29	21	9	1

*Impossible to evaluate. See text.

Although the results summarized in the table are self-explanatory, certain cases deserve special comment.

Particularly significant were the excellent results obtained with hexocyclium in one case of duodenal ulcer and another of irritable colon which previous anticholinergics had failed to help. On as little as 12.5 mg. of hexocyclium q.i.d., one patient with irritable colon improved rapidly, and was soon able to utilize a more liberal diet.

Results in one case of irritable colon were impossible to evaluate, the patient in question being extremely neurotic. In one case of duodenal ulcer, nausea was not relieved by 25 mg. of hexocyclium q.i.d., but the patient was later found to have a pyloric obstruction. Other anticholinergics were more effective in two cases of duodenal ulcer, one case of irritable colon, and the one case of diverticulitis.

The only example of any tendency towards unwanted side-effects was slight constipation and some slowing of the urinary stream in a single case. For every other patient, however, the recommended dosage of 25 mg. q.i.d. was unaccompanied by side-effects of any consequence.

Conclusions

Of the 60 cases of gastrointestinal conditions treated with hexocyclium in this investigation, results were rated excellent in 48 per cent, good in 35 per cent, and fair in 15 per cent. In one case, the results could not be evaluated.

The observations here reported suggest that freedom from side-effects represents one of the noteworthy advantages of hexocyclium.

On the basis of the present study, the most desirable dosage in the majority of cases would seem to be 25 mg. of hexocyclium 4 times a day, each dose preferably being in the form of the combination tablet which also contains 15 mg. of phenobarbital.

The effectiveness of hexocyclium, particularly in view of the low incidence and minor degree of side-effects, warrants extensive investigation of the properties of this new anticholinergic.

Summary

Hexocyclium methosulfate, a new anticholinergic, was used to treat 60 cases of various gastrointestinal conditions, mostly peptic ulcer or irritable colon.

Good to excellent results were obtained by 83 per cent of the patients.

Side-effects were infrequent and slight.

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CONSTITUTIONAL VARICES

A New Type of Noncirrhotic Esophageal Varices

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The subject of esophageal varices is most important when one considers the difficulty of management and the incidence of death associated with hemorrhage secondary to their rupture.

Esophageal varices are thought of most commonly in association with increased portal blood pressure. The increased portal blood pressure is secondary to either intrahepatic portal block or extrahepatic portal block. In addition to this, congenital esophageal varices have been described with no alteration in the portal system.

The purpose of this paper is to call attention to a new entity which hereafter shall be called constitutional varices. It is felt that this is a separate entity from congenital varices and varices secondary to intra- or extrahepatic portal block. In constitutional varices, acquired cause cannot be demonstrated.

Congenital esophageal varices that have been described in the past were found in infancy or early childhood. The constitutional esophageal varices reported here became manifest in early adult life. Heretofore, no one has described any case of generalized multiple varices which include varices of the portal venous system, as well as varices of the systemic venous system, which occurred in a young adult with no known acquired cause and no obvious congenital origin.

Case Histories

A 31-year old Negro male was admitted to the National Naval Medical Center, Bethesda, Maryland with complaints of epigastric pain, nausea and emesis of 2 weeks' duration. On physical examination he appeared well nourished and healthy, except for marked bilateral lower extremity varicose veins. On two previous hospitalizations he had had surgical treatment for these varicosities which included high bilateral saphenous ligations, and bilateral vein stripping. In spite of what was considered adequate therapy, great numbers of varicosities persisted.

An upper gastrointestinal x-ray series revealed an essentially normal esophagus, stomach and duodenum except for some spasm of the duodenal bulb. Conservative medical therapy was instituted using diet, antacids and antispasmodics. The patient did well and was subsequently discharged.

Approximately 10 days later, however, he was readmitted to the hospital. He complained again of epigastric pain, nausea, vomiting, and additionally,

of hematemesis. A repeat upper gastrointestinal series was reported as negative. The patient was sigmoidoscoped and one moderately large internal and external hemorrhoid was observed. The symptoms persisted, and subsequently the patient was gastroscoped and then esophagoscoped. Gastroscopy revealed 3 small gastric varices in the cardia of the stomach on the greater curvature, toward the posterior wall. Esophagoscopy revealed two esophageal varices in the lower third of the esophagus, approximately 4 mm. in diameter, with multiple branching tributaries (Fig. 1). A moderate esophagitis was present in the lower third of the esophagus. The mucosa was reddened and inflamed, however no bleeding point was observed. Complete hematological examination was negative. Liver function tests included cephalin flocculation, thymol turbidity, alkaline phosphatase, cholesterol and esters, total protein and A/G, prothrombin time, serum bilirubin and B.S.P. All tests were within normal limits. At no time during his hospitalization was his liver or spleen enlarged, however, a liver

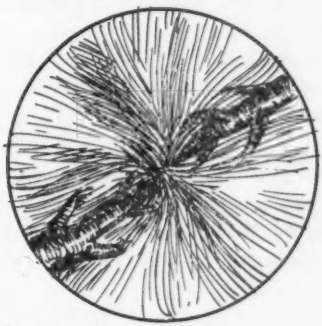

Fig. 1—This is a drawing of the esophageal varices in the lower third of the esophagus as viewed through an esophagoscope.

biopsy was performed (Fig. 2). The pathological description of the biopsy revealed normal hepatic cells and architecture, a few lymphocytes in the periportal area, and normal portal triad morphology. The biopsy section was compatible with normal liver.

He was placed on a bland diet with antacids and antispasmodics. The epigastric pain and emesis persisted intermittently for approximately 6 weeks. Intermittent hematemeses, of small quantities, continued for 6 weeks. At no time was more than one teaspoon of blood found in the emesis. The etiology of the hematemesis was believed to be associated more directly with the esophagitis than the esophageal or gastric varices.

Comment

The above case is believed to be the first of multiple varices of the portal and systemic venous systems reported in the same patient with no known

acquired or obviously congenital cause. It appears that this patient had a generally weak or a poor anatomical quality to the structure of his venous system. It does not seem to be correct to merely state that the varicosities were actually congenital in origin. That diagnosis would imply that the varicosities were present since birth. This was not the case in the above patient. The systemic varicosities did not present themselves until early adult life. The actual date of origin of the esophageal and gastric varices was unknown. It was felt, however, that they did not occur until at least early adult life. As will be seen from the literature, most true congenital esophageal varices were observed early in infancy or childhood and were manifested by hemorrhage and discovered usually at autopsy.

Vorpahl, in 1912[1], described a case of a newborn infant which died of a hemorrhage on the third day of life. At autopsy several esophageal varices were found almost resembling a hemangioma. Also Friedman[2], in 1934, described a case of a child three and one-half years old who had repeated episodes of hematemesis over an 18-month period. The child died of hemorrhage, and at autopsy esophageal varices were found with no abnormality of the liver or spleen. In 1935, Holmes and Schatzki[3], described one case of congenital esophageal varices. Subsequently, Schatzki, in 1940[4], described 116 cases of varices of the esophagus. He mentioned that there were some cases where liver and spleen were not palpable and there were no histories of liver disease. He did not, however, categorize these cases as necessarily being congenital esophageal varices. In 1944 Hansson[5], described accurately three cases of congenital esophageal varices.

Jorup[6], in 1948, however, reviewed the world literature concerning congenital esophageal varices. In his opinion, perhaps only two to three cases were bona fide congenital esophageal varices and the others were secondary to some type of acquired disease.

The question of the frequency of esophageal varices from any cause is quite difficult to determine. Brick[7], in 1955, in a series of 108 cases of esophageal varices, pointed out the discrepancy in accuracy between radiographic diagnostic technics vs. esophagoscopic methods. Of the 108 cases with esophageal varices proved by esophagoscopy, only 20 per cent were demonstrated radiographically.

Accurate autopsy material is hard to find because of the special autopsy technics and microscopic technic necessary to demonstrate varices are not well established.

Weinberg[8], in 1949, however, made observations on the occurrence of varices of the esophagus in routine autopsy material. He studied 1,189 consecutive autopsies. He found a total of 95 cases of esophageal varices. Twenty

of the cases were directly associated with cirrhosis of the liver. The remaining 75 cases he arbitrarily categorized as follows:

1. Forty-nine cases associated with coronary heart disease.

The only significance this association may have is in its relation to congestive heart failure. Since coronary heart disease is so common in the older age group, it is unlikely that there is any cause and effect relationship.

2. Twenty-six cases have been described in association with primary hepatic neoplasm, or metastatic neoplasm to the liver, or a wide variety of nonhepatogenous diseases.

Fig. 2—This is a photomicrograph of the liver biopsy. The hepatic cells and liver architecture are normal. There are a few lymphocytes in the periportal areas. Interpretation: Compatible with normal liver.

There was no cause and effect relationship in over 60 of the 95 cases reported. Of the 35 cases, in which some causal association was found, 20 were related to cirrhosis of the liver, and 15 were primarily due to some type of neoplastic involvement of the liver. It was interesting to note that bleeding from varices occurred mainly in those cases associated with cirrhosis of the liver. Only one case of noncirrhotic, unexplained type of varices bled. Palmer[9], in 1954, found esophageal varices in 4 of 7 patients with chronic heart failure, 8 of 14 with active viral hepatitis, 1 of 2 with hemolytic icterus, and 1 of 2 with amebic hepatitis. Palmer believes that in these conditions the portacaval anastomosis across the gastroesophageal junction responds quickly to an increase

in portal pressure by developing into significant varices. It has been pointed out that esophageal varices may develop after transient elevations in portal pressure, and may persist after the pressure has become normal.

Studies by Castberg[10], in 1952, have shown that chronic passive congestion of the liver predisposes to a type of real cirrhosis. This type of cirrhosis is known as cardiac cirrhosis. It may have associated esophageal varices.

Rack, and Mincks[11], in 1952 described 7 cases of esophageal varices in association with congestive heart failure, without evidence of other liver disease.

It is interesting to note that in Higgins[12], review of 115 cases of hematemesis due to varices[12], 80 per cent were in direct association with cirrhosis of the liver. The other 20 per cent were said to be related to other forms of portal hypertension, including those caused by neoplasms of the liver.

Garrett and Gall[13], in 1953, reported 13 cases of esophageal varices without typical cirrhosis of the liver. In analysing their cases, however, 3 had associated congestive heart failure; 3 had metastatic neoplasm to the liver; 1 had mediastinal Hodgkin's disease; 2 had myocardial infarcts; 1 mild portal fibrosis; 1 fatty liver; 1 suppurative hepatitis; 1 no other associated disease.

It has thus become apparent that esophageal varices are somewhat more common than had previously been thought, particularly those of noncirrhotic origin. Now one has to keep in mind that esophageal varices may be found secondary to congenital varices, cirrhosis of the liver, noncirrhotic liver disease, tumors metastatic to the liver, portal vein thrombosis, congestive heart failure, hemolytic icterus, perhaps various other causes, and now what has been newly termed "constitutional varices". The most dangerous type of esophageal varices occur in conjunction with cirrhosis of the liver. Outside of the true congenital varix, which may be quite dangerous, the other types of esophageal varices are of a more benign nature, with only a few notable exceptions.

Summary

The case reported by the author of this paper brings into focus a new entity known as constitutional varices. There is no known cause and it is believed that they represent an inherent anatomical weakness of the venous system.

It is possible that esophageal varices associated with both cirrhotic and noncirrhotic etiologies share the same type of anatomical weakness that has been stated for constitutional varices. It may, however, require minor to major physiological changes in hemodynamics, to cause manifestation of their weakness in the form of varicosities. Thus, esophageal varices may all have some constitutional anatomical weakness, and their presence depends upon the degree of anatomical weakness and the range of hemodynamic stress placed upon them.

Some individuals do not develop varicosities in spite of markedly altered venous pressures. The above explanation is one feasible reason why some people with cirrhosis never develop esophageal varicosities. There is no anatomical weakness of their veins and even though their portal pressure is quite high, they do not develop varices.

Conclusions

1. A new entity known as constitutional varices has been described. The varices are present in the esophagus and stomach. Systemic varicosities are also present.

2. The esophageal varices, and the other varicose veins associated with this condition, may be present with no known alteration in hemodynamics, but rather are directly related to the degree of anatomical weakness.

3. It is possible that other types of esophageal and gastric varices, regardless of associated etiology, are due to some degree of constitutional weakness. Usually, their presence is made manifest by alterations in hemodynamics, which may vary from minor and transient, to severe and permanent.

4. Bleeding from esophageal varices is most common in those cases associated with cirrhosis of the liver. Bleeding is rare from esophageal varices of noncirrhotic origin, except from congenital varices.

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Protocol

*Dr. Ambrose J. Hertzog**:—Case No. A—55-36, a 50-year old white Louisiana farmer, entered Touro Infirmary on 14 February 1955 complaining of fever and jaundice of three weeks' duration. Four months prior to admission he contracted a sinus infection followed by a nasal operation at another institution. With this onset he has remained ill. He reported an allergy to penicillin, aspirin and anacin.

Physical examination revealed a middle-aged, jaundiced white male, who appeared in fair condition. Blood pressure was 110/65, temperature 102 degrees F., and pulse 112. Purulent material was observed in the right nostril while the pharynx was hyperemic. Cardiac auscultation revealed a sinus rhythm free of murmurs. Moist rales were present in both lungs, particularly at the right base. The liver and spleen were not palpable.

Laboratory studies disclosed an erythrocyte count of 5.2 million; 15.4 gm. of hemoglobin; leucocyte count of 5,600 with 73 per cent neutrophiles; blood glucose of 103 mg.; NPN of 34 mg.; serum bilirubin, 4.3 mg.; a prothrombin time of 17.1 seconds as compared to a control of 14.9 seconds; negative serology, and two negative blood cultures. Thick and thin smears were negative for malaria. A heterophile agglutination test was positive 1 to 56. An EKG demonstrated low voltage. Roentgen findings revealed bilateral antral and frontal sinusitis, while on chest x-rays slight thickening of the bronchovascular markings with minimal peribronchial infiltration was noted. A gastrointestinal series was negative. Cultures of sinus material showed a coagulase positive staphyloccus aureus. Stool examinations were negative for parasites.

The patient's hospital febrile course was characterized by elevations up to 104.2 degrees F. On 16 February 1955 a course of emetine was followed with some reduction in fever, but on 21 February his temperature rose to 106.2 degrees F. rectally. The only positive finding was marked tenderness in the liver area which was enlarged from three to four centimeters below the costal edge. On 23 February a course of achromycin and erythromycin was instituted, though previous to this he had received streptomycin as well as chloroquin. On that date his condition became worse and was accompanied by vomiting of

*Pathologist, Touro Infirmary.

coffee ground material, high fever and skin petechiae. Serum bilirubin was 6.5 mg., Cephalin flocculation was negative followed a week later with 1 plus. Thymol turbidity was 6 units. Alkaline phosphatase was 16.2 Bodansky units and total serum proteins were 7.5 gm. with 3 gm. of albumin and 4.5 gm. of globulin. Febrile agglutinations were all negative. Urinalysis revealed 2 plus albumin, negative for sugar, pus cells and bacteria.

On 23 February his condition had deteriorated further. Serum bilirubin was 8.3 mg.; CO_2 was 9 mEq/l.; chlorides, 83.8; potassium 5.37 and sodium 116.6. A questionable mass was palpable in the region of the gallbladder. On 24 February an exploratory abdominal laparotomy was performed and an operative cholangiogram detected no abnormalities of the bile ducts. The gallbladder appeared normal but the right lobe of the liver was studded with firm, yellowish nodules which were biopsied. A frozen section tissue examination of the nodules was reported as inflammation and necrosis with no evidence of neoplasm.

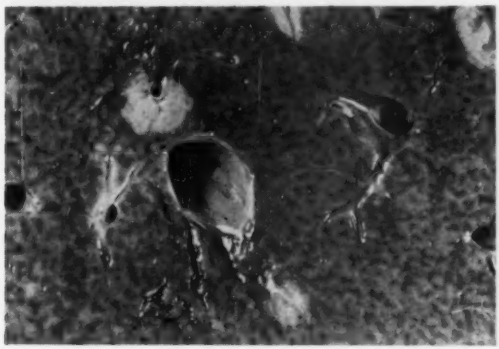

Fig. 1—Cross section of liver showing discrete greyish white nodules.

During the operation his blood pressure dropped to shock levels for which 1,000 c.c. of blood, hydrocortisone and Levophed with infusions of glucose were administered. His blood pressure rose and after two hours and forty-five minutes in the operating room he was transferred to the recovery room where his blood pressure again dropped and did not respond to Levophed. He expired at 6:05 P.M. in the recovery room.

Discussion

Dr. Blitz:—This patient had been febrile for some four months before admission to the hospital. His previous history was that of an obscure nasal and sinus infection.

On admission to the hospital everything seems to focus on the liver. The patient either had localized disease of the liver or hepatic manifestations of a systemic disease.

The physical examination is nonrevealing except for probable enlargement of the liver and associated tenderness. I can see nothing else of note in the history which would give us a clue to a diagnosis.

The laboratory studies offer some information but it may be misleading. The liver profile on admission showed an increase in serum bilirubin, although no apparent icterus was noted except by one examiner. This could have been easily missed in Touro Infirmary with our green painted walls.

After being in the hospital a few days the serum bilirubin was undoubtedly elevated to a point that clinical icterus was easily detected. The cephalin flocculation was reported as negative on admission and 1 plus a week later. The alkaline phosphatase was elevated and went up considerably with the second profile. The thymol turbidity, which was within normal limits at the beginning, also became slightly elevated. The serum proteins were a little low and while there was no reversal of the A/G ratio, the albumin component certainly was decreased. The serum protein was 5.4 gm. per cent with an albumin of 2.9 gm. per cent and globulin of 2.5 gm. The heterophile was not considered to be diagnostically positive although the first was elevated to 1/56. A second heterophile was reported as positive 1/14 and negative 1/28. The prothrombin was 15.7 seconds with a control of 13.3. This certainly would fit a normal value or at the most, a very mild hypoprothrombinemia.

During his hospital stay the patient received a number of the broad spectrum antibiotics and streptomycin, as well as a trial with amebacidal therapy, including one grain of emetine daily for 5 days and chloroquin.

In the face of an obscure hepatic condition associated with a febrile state, it is justifiable to administer this type of therapy empirically.

He did very poorly, however, and his jaundice increased. Since the jaundice was thought to be obstructive, surgical exploration of the patient was decided upon.

At operation nothing was found except the nodules in and on the surface of the liver. One or two of these were biopsied showing inflammatory reaction and necrosis. We must assume that everything else in the abdomen was negative and that extrahepatic obstruction was ruled out.

The man died shortly after surgery. Shortly before death a marked acidosis, hyponatremia and hypochloremia developed.

In this problem it is of primary importance to differentiate between hepatocellular and obstructive jaundice. If obstructive jaundice, it becomes necessary to determine whether it is intrahepatic or extrahepatic.

This man did not appear to have hepatitis, either infectious or chemical. From the laboratory standpoint we can safely conclude that he had an obstruc-

tive type of jaundice. The only thing in favor of hepatocellular involvement, with associated obstructive phenomenon, is the positive cephalin flocculation. Ordinarily, in so severely ill a patient with this much jaundice, if hepatocellular involvement were present, it would be rare to have a negative cephalin flocculation. On occasion we have seen patients with hepatitis with a negative cephalin flocculation or possibly a 1 plus. With any amount of involvement of the liver, however, where the intrinsic structure is involved, the cephalin flocculation is usually positive. Another point in favor of this being an obstructive type of jaundice is the high alkaline phosphatase which increased considerably in a very short time. This is characteristic of all types of obstructive jaundice, whether intrahepatic or extrahepatic in origin. Another type of liver involvement that will give a high alkaline phosphatase is malignancy, usually metastatic. Some of the highest values that I know of have been in patients who have had

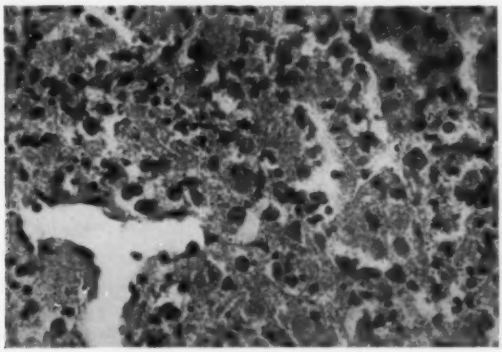

Fig. 2—Photomicrograph of liver nodule showing extensive necrosis with neutrophilic exudate.

diffuse metastasis to the liver, some with and some without obstructive phenomena.

At operation it was evident that extrahepatic obstruction was not present. A thorough exploration failed to reveal any abnormality of the gallbladder and extrahepatic biliary ducts. Therefore, we conclude that this is an intrahepatic obstruction.

What causes intrahepatic obstruction? A process in the small or large bile radicles or in the cholangiolar system can cause the obstruction. If not within the bile radicles, abnormalities within the liver can cause pressure and obstruction (extraluminal) to the biliary system. Listed on the blackboard is the differential diagnosis for this problem. Since we are considering intrahepatic obstruction we shall first consider neoplasms. Diffuse hepatic metastatic malignancy, if present, would have to exert pressure on the biliary system. Hodgkin's and allied diseases of the liver would be unusual if this was the only organ involved

because it is part of a generalized disease. I do not think that Hodgkin's disease can be seriously entertained as the primary lesion judging from the pathology observed at operation. Both metastatic malignancy and Hodgkin's disease can cause prolonged fever. The white blood count was 5,000 and 7,000 on two occasions which could occur with either one of these conditions. Usually, in febrile states associated with metastatic malignancy to the liver, leucocytosis is generally observed. Some of the highest white counts are observed in metastatic liver disease, especially if there is involvement of the liver capsule.

Consideration of acute inflammatory disease includes amebiasis. Amebiasis cannot be called an acute lesion but chronic involvement of the liver with acute manifestations usually causes the picture considered here. I know of no other acute infectious process capable of producing intrahepatic obstruction with a low white count and fever over a period of four months.

Pyogenic infections must be considered as a very important and possible cause of this man's death. Had chills and a more elevated white count been present, serious consideration could be given to a suppurative pyelophlebitis with multiple abscesses in the liver caused by a variety of conditions in the abdominal cavity, such as a ruptured diverticulum or ruptured appendix. Liver abscesses are seen often in ruptured appendicitis and the diagnosis may remain obscure for a long time. With any other type of pyogenic infection, such as a cholangitis, the cause would remain undetermined. It might be difficult to see why a patient should develop cholangitis with multiple areas of obstruction without any other definite antecedent cause, and to conceive that the operative finding of multiple nodules which apparently were scattered throughout the liver and surface could be due to pyogenic infection.

We should now consider granulomatous diseases and Hodgkin's is sometimes classified as one of the granulomatous conditions. Another granulomatous condition that we must consider is sarcoidosis. This, with its protean manifestations, can cause almost any type of clinical picture. I am unaware of cases where sarcoid of the liver was found without involvement elsewhere, although there is questionable involvement of the lung. It is very possible that the picture of the left paracardiac region with increased bronchovascular markings and evidence of bronchiectasis may be a clue to the diagnosis. This may be part of a general systemic condition with hepatic involvement. There was no evident adenopathy and the prolonged febrile course usually does not go along with sarcoidosis; but that doesn't rule it out. A valuable method for the diagnosis of obscure lesions or sarcoid is by liver biopsy. The percentage of positives in previously unconfirmed or unverified cases is probably higher with a liver biopsy, either with needle puncture or open laporotomy. Recently we have focused our attention on the scalene nodes. Some workers feel that the scalene nodes offer a positive diagnosis more often than liver biopsy. Personally, I do not feel that the results are as good.

We cannot rule out tuberculosis. In a long illness with a septic fever tuberculosis must always be considered. The possibility of a miliary or sub-miliary type of involvement has to be given serious consideration.

Mycotic infections which are related in their clinical manifestations to tuberculosis and sarcoid disease have a different etiology. On the blackboard I have listed some of the main suspected types of mycotic infection although some can be ruled out rather quickly. A generalized nocardiosis can act exactly like a disseminated miliary or submiliary tuberculosis and sarcoid infection. Histoplasmosis can act the same way. Histoplasmosis of the liver alone, however, without definite evidence in the pulmonary fields is very rare. In fact, I know of no such cases.

Blastomycosis, aspergillosis and actinomycosis are to be mentioned without serious consideration. Actinomycosis usually doesn't form small abscesses or small nodules as was found in this case. Aspergillosis, at times, may form abscesses if there is a diffuse or disseminated spread. Usually, however, there is pulmonary involvement. Blastomycosis is usually not in the liver alone, and certainly there should be some evidence of pulmonary involvement.

Although I have listed a number of conditions, I still do not know the exact diagnosis that would fit any one of these conditions. Either we haven't enough information for a diagnosis or else we can find a loophole with most of these conditions, some of which cannot be ruled out.

Metastatic malignancy can be ruled out from the sections obtained at operation. Hodgkin's disease cannot be ruled out but more than likely this is not the diagnosis. It is rare to see a pyogenic infection involve the liver in a patient that does not have chills and a septic temperature with leucocytosis.

Mention is made in the protocol concerning a nasal and sinus infection. It is possible that he may have had a staphylococcus septicemia with multiple abscess formation in the liver and for some reason or other a low white count. If he had a septicemia and a blood culture which was negative due to suppressant antimicrobial therapy before, I do not think the liver would be the only organ involved. More than likely, when a patient has a diffuse involvement of the liver with a staphylococcus septicemia, in all probability the kidneys would also be involved. It is difficult to make the diagnosis of multiple abscesses of the kidney unless we have more information, and more often than not the diagnosis is suspected and made only at autopsy. We cannot rule out pyogenic infections, but there is a possibility that one of the unusual types of multiple abscesses of the liver may be the cause of death.

It is difficult to make a specific diagnosis of the granulomas. It is better to make a diagnosis of a disseminated granulomatous lesion unless you have definite, specific evidence. In tuberculosis, the presence of a suspected disseminated granulomatous condition requires treatment for tuberculosis with specific drugs

that will affect this disease alone and not mask any other infection. A drug of the isoniazid group would be the one of choice because of our recent favorable experiences with isonicotinic acid. If, however, such a patient is given streptomycin we may obscure some other bacterial disease.

We can group these conditions and say that the patient may have had a diffuse granulomatous disease although sarcoidosis has been ruled out by the section of tissue. If we must make a diagnosis, I would select one of the diffuse granulomatous diseases as the cause of this patient's death.

Dr. Hertzog:—Thank you, Dr. Blitz. Dr. Threefoot has summarized the diagnoses made by the Tulane University students.

Dr. Threefoot:—As primary diagnoses three students selected hepatic amebiasis; two chose subacute or chronic infectious hepatitis; one chose cholangitis with multiple liver abscesses, etiology unknown; one chose an obstructive type of jaundice with malignancy and one selected actinomycosis. As secondary diagnoses, two were infectious hepatitis and one actinomycosis.

Dr. Hertzog:—I'm going to ask Dr. Craighead to reveal his observations at operation.

Dr. Craighead:—I would take exception to one remark Dr. Blitz made, that is, the feeling of confidence that the surgeon has after he has explored such an abdomen. In this particular instance, however, there was nothing in the head of the pancreas to suggest a pancreatic malignancy.

At times we have run into a great deal of difficulty in making a diagnosis of lesion in the head of the pancreas. I recall one patient who over a period of four years was operated on four times for a suspected lesion. He had jaundice and mild bleeding from the gastrointestinal tract. He also had cholelithiasis, but it wasn't until he developed nodules in the umbilicus and was moribund that the diagnosis was made. His last operation had been five months previously.

The diagnosis of malignancy in such patients is sometimes difficult. This also applies to a patient who has mild jaundice and is explored. You suspect that he has carcinoma of the head of the pancreas, but his common and pancreatic ducts are not particularly dilated. A small lesion in the head of the pancreas is practically impossible to recognize.

At operation he did have multiple lesions of the liver, and my first thought was carcinoma of the pancreas. We could, however, find nothing to suggest it and x-ray dye studies were negative. The preoperative prothrombin time was a little low and at surgery the patient bled quite a bit. His blood pressure dropped before much blood loss which continued. During operation adrenal extract and blood improved his blood pressure.

Postoperatively, in the recovery room, his blood pressure dropped markedly but responded quickly to blood and Levophed. After restoring his blood pressure

with blood he continued to have Levophed; but a patient who is bleeding will not have a beneficial response to Levophed.

Pathological Discussion

Dr. Hertzog:—At autopsy, this middle-aged man was well developed and well nourished. He had not lost any appreciable amount of weight but he was markedly jaundiced.

The first impression of the liver is that of widespread disseminated carcinomatosis because there were white nodules on the surface of the liver.

The immediate cause of death was bleeding into the abdominal cavity where 1,500 to 2,000 c.c. of fresh blood was noted.

The liver was enlarged and weighed 2,100 gm. It revealed a discoloration that we associate with jaundice, i.e., a dark, brownish-yellow color. Other photographs show the nodules a little better and they are not quite as discrete as seen in a carcinomatous nodule (Fig. 1). They are rather diffusely disseminated throughout the liver and, as mentioned on the protocol, we were quite surprised when we looked at it microscopically and found that they were not carcinoma.

There was widespread necrosis in the nodules (Fig. 2), and some areas were rather sharply demarcated. The parenchymal liver cells have a fairly normal appearance and Dr. Blitz is quite right in saying that this is not an hepatocellular type of jaundice. Although we found later some enlarged lymph nodes in the region of the head of the pancreas we have no real explanation for the jaundice other than the nodules and the inflammatory process in the liver. It is an intrahepatic type of jaundice. Other photographs show some of the inflammatory process on the edge of the necrotic nodules and neutrophilic exudate but there was nothing specific about the findings.

When we find this type of inflammation a careful search is made for fungi. We have a very good stain today, a Schiff's periodic acid stain, which helps to bring out fungi very strikingly, which we tried but were unable to demonstrate any fungi.

We also attempted to culture the nodules in the inflammatory areas, both aerobically and anaerobically and on fungus media such as Sabouraud's media, but we were unable to grow any fungi.

Besides the liver, the spleen, which was not palpable and weighed 165 gm., contained a number of these granulomatous nodules. This slide is an area of the spleen showing a necrotizing granulomatous lesion. A certain amount of angiitis was present. In no sections of the liver, spleen or kidneys, however, did we find anything suggestive of *periarteritis nodosa.*

The adrenal gland on the left was enlarged and shows a nodule about the size of a quarter. Here is a section through that nodule which likewise shows

the necrotic granulomatous lesion. The next slide shows this inflammation extending out into the capsule of the adrenal gland. There is nothing striking about this lesion. There is no evidence of tubercles as you see in tuberculosis or sarcoidosis. There are no giant cells which we associate frequently with fungus infection, particularly blastomycosis. There is only a diffuse necrosis with associated inflammation of the periphery.

The question of Hodgkin's disease comes up and we would consider a Hodgkin's granuloma rather than a Hodgkin's sarcoma. The picture of Hodgkin's granuloma, however, is not similar to this. We would expect to see fibrosis, eosinophils and Dorothy Reed cells. There is only a suggestion of a Dorothy Reed cell and it is not multinucleated. There are no eosinophiles present. Hence, it does not make a good Hodgkin's granuloma.

There were several lymph nodes in the region of the head of the pancreas that were about 2 cm. in size and these showed similar necrotic granulomas.

The lungs showed nothing other than edema and the granulomatous lesion was absent.

Summary and Conclusions

In summary, we have a case that anatomically is manifested by multiple necrotizing granulomas involving principally the liver, and in addition, the spleen, left adrenal, and the regional lymph nodes of the liver. From an anatomical standpoint, the diagnosis is granuloma of unknown type. We attempt to make an etiological diagnosis whenever possible, but we were unsuccessful in obtaining any helpful bacteriological etiology.

Research of the literature for a similar lesion revealed an article of about 20 years ago by Beaver and Snell[1]. They, for want of a better etiological diagnosis, considered these cases as possibly atypical manifestations of Hodgkin's disease. You can, however, raise many objections to this because it is using the diagnosis as a waste basket.

In recent years there has been a tendency to emphasize hypersensitivity as an etiological factor in certain inflammatory processes including *periarteritis nodosa*. Hypersensitivity is something to think about in this case. This man had a history of hypersensitivity to penicillin. I think that we cannot rule out altogether the possibility of some type of allergic granulomatous inflammation. We are all familiar with the necrosis of tissue associated with the Arthus phenomena.

I think this case also illustrates the limitations of histological diagnosis. We can make an anatomical diagnosis but we cannot always make an etiological diagnosis.

Our final anatomical diagnosis then is multiple granulomatous lesions of unknown etiology.

A pathologist should more often make a diagnosis of a granuloma of unknown etiology rather than try to guess the nature of the etiological agent. When we cannot find an organism by stains or cultures we are usually guessing in the etiological diagnosis in cases of granulomas. We should not hesitate to say that we don't know the cause of many of these lesions.

Dr. Blitz:—This patient displayed what I thought was an intrahepatic type of obstruction wherein the small bile ducts were obstructed extramurally by these small nodules. If enough of these small radicles are involved, you certainly can have the obstructive intrahepatic phenomenon, even though you don't have gross obstruction to large biliary radicles. Although ignorant of the diagnosis I classified Hodgkin's disease with the granulomatous lesions.

REFERENCE

1. Beaver, D. C. and Snell, A. M.: Nodular Granulomatous Lesions of the Liver, Spleen and Lymph Nodes. J. Lab. & Clin. Med., **20**:2-12, 1934.

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President's Message

On Objectives

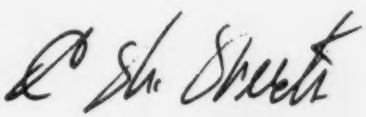
Two of the major annual objectives of the College were gained once more as the 1957 scientific session and the postgraduate course drew to a close in Boston, 23 and 26 October respectively.

We are indeed indebted to Dr. Henry Baker and his committee who invited us to meet in a city that is a world-renowned seat of learning and who labored over a good portion of the year to invite understanding speakers and to arrange the program.

An excellent opportunity of learning new facts and broadening one's point of view was provided by the 30 presentations in the scientific session on a variety of gastrointestinal subjects. In the postgraduate course there was an equal coverage of subject matter by the 31 speakers but stress was placed on basic diagnosis and treatment. Surely in this week of activity there was a unique opportunity for the exchange of ideas by both formal and informal discussion and the College collectively can feel a sense of accomplishment in this undertaking.

One closely related objective remains to be reached. This is the publication in our journal of the papers and the discussions of the meeting. The importance of giving to those who attended the meeting, as well as those who did not, a critical record of the transactions is second only to the meeting itself.

To assist in the accomplishment of these objectives we should not lose sight of the considerable expenditure of time and effort made by the administrative section of the College with its 10 standing committees which met for two days before the scientific session opened and at various intervals during the year. Among the many topics that required consideration were those of finance, membership, research; improvements in our publication and next year's meeting in New Orleans were discussed *in extenso*. Solutions to these problems are some of our future objectives.



NEWS NOTES

Future College Meetings

We list below the dates and places of future meetings of the American College of Gastroenterology:

23rd Annual Convention, New Orleans, La., 19-25 October 1958.

24th Annual Convention, Los Angeles, Calif., 20-26 September 1959.

25th Annual Convention, Philadelphia, Pa., 23-29 October 1960.

26th Annual Convention, Cleveland, Ohio, 22-28 October 1961.

College Officers for 1957-1958

At the Annual Meeting of the American College of Gastroenterology held in Boston, Mass., on Sunday, 20 October 1957, Dr. Frank J. Borrelli of New York, N. Y. became the President-elect. He will assume the Presidency at the Annual Meeting to be held in New Orleans, La., October 1958.

At the Annual Banquet on Tuesday, 22 October 1957, Dr. C. Wilmer Wirts of Philadelphia, Pa., assumed the Presidency, succeeding Dr. Arthur A. Kirchner of Los Angeles, Calif.

Drs. Joseph Shaiken, Milwaukee, Wisc.; Henry Baker, Boston, Mass.; Louis Ochs, Jr., New Orleans, La. and Edward J. Krol, Chicago, Ill., were selected as Vice-Presidents. Dr. Theodore S. Heineken of Glen Ridge, N. J. was re-elected Secretary.

Trustees elected for a full three-year term are: Drs. I. R. Jankelson, Boston, Mass.; S. Bernard Kaplan, Newark, N. J.; Lionel Marks, Toronto, Canada; John M. McMahon, Bessemer, Ala. and George K. Wharton, Los Angeles, Calif. Re-elected for one year to complete unexpired terms are: Drs. Harry Barowsky, New York, N. Y. and Robert R. Bartunek, Cleveland, Ohio.

Drs. Samuel W. Yabroff, San Francisco, Calif.; Dale W. Creek, Santa Barbara, Calif.; Max Caplan, Meriden, Conn.; Irving A. Levin, New Orleans, La.; Charles W. McClure, Boston, Mass.; Joseph R. Van Dyne, Forest Hills, N. Y.; Stanley S. Sidenberg, Cleveland, Ohio; Julian A. Sterling, Philadelphia, Pa. and Fernando Milanes, Havana, Cuba were elected Governors.

At the Annual Meeting of the Board of Governors of the College held on Tuesday, 22 October 1957, Dr. Henry G. Rudner, Sr., Memphis, Tenn., was re-elected Chairman of the Board of Governors. The Board of Trustees on Wednesday, 23 October 1957, elected Dr. Arthur A. Kirchner as their Chairman.

Re-appointed by the Board of Trustees were Dr. Lynn A. Ferguson, Grand Rapids, Mich., Secretary-General; Dr. William C. Jacobson, New York, N. Y., Treasurer and Dr. Samuel Weiss, New York, N. Y.; Editor-in-Chief.

The President, Dr. C. Wilmer Wirts, appointed Dr. Maxwell R. Berry of Atlanta, Ga. and Dr. A. Jack Tannenbaum of Greensboro, N. C. as Governors for their respective states.

1957 Ames Award

The American College of Gastroenterology takes pleasure in announcing that the 1957 Ames Award for the best paper published during the past year in its official publication, The American Journal of Gastroenterology, was awarded to Dr. Bernard S. Wolf of New York City.

Dr. Wolf is the Director of the Department of Radiology at The Mt. Sinai Hospital and Associate Clinical Professor at Columbia University, College of Physicians and Surgeons. The title of Dr. Wolf's award winning paper is "Roentgen Examination of the Esophagus".

The award was presented at the Annual Banquet of the College and was accepted for Dr. Wolf by Dr. Frank J. Borrelli, President-elect of the College.

International Academy of Proctology 1957-1958 Award Contest

The International Academy of Proctology announces its Annual Cash Prize and Certificate of Merit Award Contest for 1957-1958. The best unpublished contribution on proctology or allied subjects will be awarded $100.00 and a Certificate of Merit. The winning contribution will be selected by a Board of Impartial Judges, and all decisions are final.

The formal award of the First Prize, and presentation of other Certificates, will be made at the Annual Convention Dinner Dance of the International Academy of Proctology, 11 April 1958, at the Hotel Del Prado, Mexico City, Mexico.

The International Academy of Proctology reserves the exclusive right to publish all contributions in its official publication, *The American Journal of Proctology*. All entries are limited to 5,000 words, must be typewritten in English, and submitted in five copies. All entries must be received no later than 1 February, 1958. Entries should be addressed to: Alfred J. Cantor, M.D., International Secretary, International Academy of Proctology, 147-41 Sanford Avenue, Flushing, New York.

Course in Gastroenterology

Gastroenterology, a two-day Postgraduate Course, has been announced for 15 and 16 January, to be presented at the University of Kansas Medical Center, Kansas City, Kansas.

Patient material of representative problems is presented and constitutes an important part of the program. The informal symposium and panel method of teaching is utilized. The panels include surgeons as well as internists for comprehensive coverage of selected gastrointestinal problems.

Further information concerning details of the course, fee, registration, etc., may be obtained by writing the Department of Postgraduate Medicine, University of Kansas School of Medicine, Kansas City 12, Kansas.

New Medical Journal

Perspectives in Biology and Medicine, a new quarterly journal dedicated to a multidisciplined approach to the problems of biology and medicine, is announced by the Division of Biological Sciences and the Press of the University of Chicago.

Appearing in the first issue are "Ten Years of Creative Group Therapy" by George Day, Former Medical Superintendent of the Mundesley Sanatorium, Norfolk, England; "Non-Endocrine Aspects of Stress" by M. S. Goldstein, Michael Reese Hospital, and Estelle R. Ramey, Georgetown University School of Medicine; "Medical Teaching by a Non-Medical Specialist" by C. Judson Herrick, Professor Emeritus of Neurology, University of Chicago; "Some Considerations Regarding Biochemical Genetics in Man" by Herman M. Kalckar, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland; "Speculations on the Action of Insulin" by Maurice E. Krahl, Professor of Physiology, University of Chicago; "Freud's Legacy to Human Freedom" by Lawrence S. Kubie, Yale University School of Medicine, New York Psychoanalytic Institute, and College of Physicians and Surgeons of Columbia University; "A Critical Look at Medical Education in the United States" by Russell Meyers, State University of Iowa Hospitals; and "Normal Young Men" by Roger J. Williams, Biochemical Institute, The University of Texas.

The outstanding editorial board of *Perspectives* includes William B. Bean, Medicine, State University of Iowa; N. J. Berrill, Zoology, McGill University; Paul R. Cannon, Pathology, University of Chicago; Frank L. Engel, Medicine, Duke University; George L. Engel, Psychiatry, University of Rochester; Maurice S. Goldstein, Michael Reese Research Institute; James V. Neel, Heredity Clinic, University of Michigan; Irvine H. Page, Research Division, Cleveland Clinic, Theodore Rasmussen, Neurosurgery, McGill University; S. L. Washburn, Anthro-

pology, University of Chicago; and Alfred E. Wilhelmi, Biochemistry, Emory University.

Subscriptions, at $6.00 a year, may be sent to The University of Chicago Press, 5750 Ellis Avenue, Chicago 37, Illinois.

American Board of Internal Medicine

Dr. Julian Meade Ruffin, Professor of Medicine, Duke University School of Medicine, Durham, North Carolina, has accepted his election as a member of the Subspecialty Board in Gastroenterology for a term of five years beginning 1 July 1957.

Dr. Ruffin will replace Dr. Leon Schiff whose term expired July 1, 1957.

American Academy of General Practice

The American Academy of General Practice Tenth Annual Scientific Assembly will give more than 8,000 family doctors, residents, interns and guests an opportunity to hear 35 medical experts discuss subjects ranging from teen-age problems to old-age problems and from heart disease and ulcers to eye ailments, fractures and the hypnotized patient. The four-day Assembly opens 24 March in the new Dallas Memorial Auditorium.

More than 90 scientific and 300 technical exhibits will supplement the scientific lecture program.

Special activities are planned for the Academy's tenth anniversary Assembly. Tuesday, 25 March will be Dallas Southern Clinical Society Day. The DSCS meeting, held each March in Dallas, has this year been combined with the AAGP Assembly.

The Academy's policy-making Congress of Delegates will convene at 2 P.M. Saturday, 22 March. All sessions of the Congress and many social functions will be held in the Statler Hilton hotel.

Wednesday evening, 26 March following induction ceremonies for Academy President-elect Holland T. Jackson, Ft. Worth, Tex., more than 3,000 guests will attend a president's reception and dance honoring Dr. Malcom E. Phelps, El Reno, Okla., president of the Academy.

In Memoriam

We record with profound sorrow the passing of Dr. Louis H. Merker of Bronx, N. Y., Fellow of the American College of Gastroenterology. We extend our deepest sympathy to the bereaved family.

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GASTROINTESTINAL TRACT

COEXISTING HISTOPLASMOSIS AND TUBERCULOSIS OF THE ALIMENTARY TRACT: J. W. Peabody, Jr. and Howard A. Buechner. Am. J. Med. 21:143 (July), 1956.

The case of coexisting tuberculosis and histoplasmosis of the alimentary tract is presented. Tuberculous involvement of the esophagus, small intestine and colon was unusually extensive and severe, with death resulting from esophageal and ileal perforations. A single ulceration attributable to histoplasmosis was apparently confined to the oral cavity and benign in its behavior. The lesion underwent spontaneous regression and does not appear to have contributed to the events leading to the patient's demise. As a result, the authors suggest that it would seem advisable to be extremely cautious in evaluating the effectiveness of various therapeutic measures in the disease which is often benign and which may undergo a spontaneous regression. The first evidence of histoplasmosis became manifest just after 21 consecutive months of hospitalization and treatment for active pulmonary tuberculosis.

JOHN M. MCMAHON

GASTROINTESTINAL BLEEDING OF UNKNOWN ETIOLOGY: Jack E. Tetirick. Ohio M. J. 52:1184 (Nov.), 1956.

This is a follow-up study of 86 patients (46 male and 40 female) who were admitted to the Massachusetts General Hospital from 1947-1953 with a diagnosis of gastrointestinal hemorrhage and who were discharged without a definite diagnosis as to the source of the bleeding. Eighteen of the 86 patients (21 per cent) eventually had a source of hemorrhage proven, the most common resulting diagnosis being gastritis. Of the cases in which the diagnosis was eventually established, 11 cases or 61 per cent had gastritis, 2 cases or 11 per cent had duodenal ulcer and one each had multiple telangiectases, neurofibroma of the duodenum, gastric ulcer, gastric carcinoma and traumatic erosion of the gastric mucosa.

Every patient had an upper gastrointestinal series and half had two or more such examinations without revealing the source of the hemorrhage. Five patients with duo-

denal deformity by x-ray had a source other than duodenal ulcer as the proven origin of the hemorrhage. Exploration in an attempt at diagnosis was employed in 9 cases with no diagnosis being revealed in 6 cases. However, in 4 of these 6 cases a subtotal gastrectomy was performed with three of the stomachs showing gastritis and the fourth a traumatic erosion of the gastric mucosa. The author concludes that an aggressive attempt should be made at the first admission to establish the source of hemorrhage early in gastrointestinal bleeding.

ARNOLD STANTON

DIGESTIVE ULCER, A DISEASE TO BE CONSIDERED UNQUESTIONABLY HEREDITARY (RECESSIVE INHERENCE IN PREDISPOSITION): J. J. Dubarry and Ch. Pisot. Presse medicale 64:1857-1858 (Nov.), 1956.

It has been admitted by all clinicians that digestive ulcer may possibly be an hereditary and familial disease in certain cases at least. Yet the authors were able to demonstrate, as a consequence of a statistical study and the reckoning of chances by application of the genetic laws, starting from an inquiry into the history of 50 families with 800 cases of digestive ulcer, that: in fact the condition is always hereditary. This inheritance shows recessive characteristics; it carries the involvement of two pairs of genes, of which one is connected to the sexual chromosome (and this explains the masculine predominancy: 4 men versus 1 woman), so that we are led to admit that the ulcerous disease is revealed by adjunction to the hereditary factors of such other factors as are particular to the individual or originating from the environment, a point which will be studied by the authors in a further paper.

Finally, it is not impossible that such cases of gastroduodenitis as apparently primary pseudoulcerous, be relevant to similar recessive heredity, but with some variation in the significance of the anomaly (variation in specificity) or with involvement of a single pair of genes.

GUY ALBOT

ESOPHAGUS

RADIOTHERAPY OF CANCER OF THE UPPER ESOPHAGUS: S. Nemours-Auguste. Arch. mal. app. dig., 45:336 (Apr.), 1956.

This is a presentation of three cases of cancer of the upper end of the esophagus, raising points for discussion from the point of view of diagnosis, evolution and therapy.

If the esophagoscopy and radiology are positive and the biopsy negative, act as for cancer without wasting precious time.

One patient is still living three years and two months later without a relapse after radiotherapy. A second patient, alive two years and ten months after radiotherapy, has at present a bronchopulmonary extension which is being treated. The third patient shows no benefit.

The author believes that these cancers are indebted to curative radiotherapy exclusively and considers it preferable to perform a gastrostomy before treatment by radiotherapy.

CARCINOMA OF THE ESOPHAGUS: Rafael Alascio. J. Internat. Coll. Surgeons, 26:500 (Oct.), 1956.

The author reports on 240 cases of esophageal carcinoma observed from 1950 to 1955.

Two hundred four patients were men, only 36 women.

The lower portion of the thoracic segment is the most frequent site of location.

Of those 240 cases only 40 cases were considered clinically operable.

The author establishes two early syndromes of this disease, namely a daily and rhythmic pain associated with eating, which may or may not be associated with a burning in the esophagus and stomach.

The second early feature is intermittent dysphagia. After having ruled out biliary or other upper gastrointestinal disease the author recommends frequent examinations of the esophagus by both x-ray and endoscopy. This way an early diagnosis can be established and a successful resection made possible.

H. J. JOSEPH

CHRONIC ESOPHAGITIS: Earle B. Kay and Frederick S. Cross. Arch. Int. Med., 98:475, 1956.

Any chronic irritation or inflammation of the esophagus may lead to cancer formation, i.e., prolonged intake of hot tea by Scotch females or Russian Jews, or hot rice by Chinese males; of alcohol, also scars from syphilitic esophagitis, from lye burns, strictures of various origin, diverticula, hiatus hernia and achalasia may predispose to malignancy. Ten patients are reported with chronic esophagitis diagnosed by esophagoscopy who subsequently developed carcinoma. Seven of these had associated hiatal hernia, two diverticula and one achalasia.

H. B. EISENSTADT

STOMACH

HEMATEMESIS AND MELENA IN CAMBRIDGE (ENGLAND): A. P. Waterson. Am. J. Digest. Dis. 1:193-205 (May), 1956.

An analysis is made of 170 consecutive admissions for hematemesis and melena in a period of 20 months. Of these, 154 cases were regarded as due to ulcer disease. The mortality was 15 or 9.7 per cent. Noted by the author was the increasing proportion of middle-aged and elderly men as well as the almost complete disappearance of the acute gastric ulcer of young women as a source of serious gastric hemorrhage. Included in the 154 cases of bleeding due to ulcer were 34 cases in which no ulcer was demonstrated on x-ray studies but shallow acute gastric ulcer was considered the causative agent on the basis of history and clinical impression.

WALTER CANE

COLORED PHOTOGRAPHS THROUGH FLEXIBLE GASTROSCOPE BY THE MEANS OF AN ELECTRONIC FLASHLIGHT: Ch. Debray and P. Housset. La Semaine des Hopitaux de Paris 32:237-243 (June), 1956.

Photomaking *through* the gastroscope is a choice method for it admits selection in the pictures to be taken.

The author's apparatus consists in a slightly modified gastroscope, provided with a minute built-in electronic flashlight, introduced at the same time. An incandescent lamp is annexed for common examination. The electronic flashing lasts only one thousandth of a second and is very actinic. It allows color photography. Every caution has been taken, when building such an apparatus, so as to ensure complete safety both for patient and examiner.

A description follows of the author's routine technic, and first results brought by such methods are stated.

The procedure seems an interesting one, both as a didactic and a material improvement.

GUY ALBOT

VAGOTOMY AND GASTROENTEROSTOMY IN THE SURGICAL TREATMENT OF DUODENAL ULCER: K. R. Trueman and D. L. Kippen. Canad. M.A.J., 75:547 (1 Oct.), 1956.

One hundred and five patients (25 women) with peptic ulcer symptoms were subjected to vagotomy and gastroenterostomy because of failure of standard medical measures or for economic expediency.

Results were followed for 3 to 10 years

and tabulated in good, fair or poor categories.

Since 82.8 per cent of these patients obtained good results, the authors feel that this surgical approach justifies itself on the basis of ulcer control, low mortality and freedom from postoperative complications.

A. M. SUSINNO

GASTRIC ULCERS: J. H. Geddes, W. N. Downe and J. A. Taylor. Canad. M.A.J., 75:550 (1 Oct.), 1956.

Since the ideal management of gastric ulcers has remained a controversial subject for half a century, 100 cases were analyzed with follow-ups 2 years or more.

Thirty patients were subjected to surgery and the remaining 70 were medically treated.

Since only one of the entire series and this in the operative group developed carcinoma, it is concluded that surgery is not warranted for all patients with gastric ulcers.

While there are no absolute criteria to distinguish benign from malignant ulcers, the authors feel that careful evaluation of a gastric ulcer patient hospitalized for 3 to 6 weeks should lead to an error less than 3 per cent.

The low incidence of malignant ulcers in this series as against the 5-10 per cent in other series is believed to be due to the fact that this hospital is not a referral center but one that deals with the average ulcer patient who ordinarily presents himself to the generalist.

A. M. SUSINNO

GASTRIC SURGERY IN LOCAL HOSPITALS: A. Gaum and D. Gaum. Canad. M.A.J., 75:555 (1 Oct.), 1956.

The low postoperative mortality of 3.7 per cent in a series of 132 subtotal resections for peptic ulcers or carcinoma carried out in two small Australian hospitals prompted analysis of minimum requirements for successful operation on the stomach.

The authors list 8 factors they believe accounted for their results which compare equally well with those current in large clinics. By following these principles gastric surgery in their opinions can be adequately performed in small hospitals.

The minimum prerequisites listed are: 1. accurate diagnosis 2. careful judgment in the choice of patients for surgery 3. meticulous preoperative preparation 4. availability of antibiotics 5. availability of blood for transfusion 6. employment of established surgical technics resulting from the newer understanding of gastric physiology 7. satisfactory anesthesia 8. careful postoperative management, based on knowledge and correction of electrolyte, protein and vitamin deficiencies.

A. M. SUSINNO

SUBTOTAL GASTRECTOMY FOR PEPTIC ULCER, POSTOPERATIVE RESULTS IN 177 CASES: George B. Long, Norbert E. Medved, Richard D. Wilson and Gerhard O. Bern, Am. J. Digest. Dis. 1:407-416 (Oct.), 1956.

In an effort to evaluate the results of subtotal gastric resection for peptic ulcer at the Veterans Administration Hospital in Portland, Oregon, a series of 177 subtotal gastrectomy cases is reviewed. Of the five postoperative deaths, four occurred in cases of medically intractable massive gastric hemorrhage while the fifth case was the result of myocardial infarction during the operation. On the remaining 172 patients the authors evaluate results in terms of weight regained, strength regained, absence of dumping syndrome, and absence of recurring ulcer. Among the three groups of patients admitted for elective surgery, by reason of obstruction, hemorrhage, and intractability, the third group showed results markedly below the first and second groups. The authors rightly conclude that the third group includes the intractable individual as well as the intractable ulcer and that lack of willingness to postoperative readjustment is commensurate to lack of willingness to preoperative dietary cooperation.

WALTER CANE

INTESTINES

SURGICAL TREATMENT OF ULCERATIVE COLITIS: Warren W. Francis and Normand E. Gauvin. Rhode Island M. J. 39:502 (Sept.), 1956.

This article reviews the experience in the surgical treatment of ulcerative colitis at the Rhode Island Hospital from 1951 through 1956.

A total of 18 or 22 per cent of patients were treated with a mortality of 33 per cent or 6 postoperative deaths. Twelve patients were females and the average was 42 years. The average duration of symptoms prior to surgery was four to seven years. Medical treatment consisted of varying amounts of dietary, antibiotic steroid, antispasmodic and physiotherapy.

The primary indications for surgery were intractable disease in 16 patients, perineal fistulas and abscesses in one case and perforation, hemorrhage and obstruction in one case. The secondary indications were carcinoma in one patient, pseudopolyposis in three, and rectal fistula in five patients.

One patient had a vagotomy with temporary relief. All the 18 patients had either an ileostomy alone or combined with colectomy or abdominoperineal proctosigmoidectomy in one, two or three stages. All but two of the patients had serious complications. Seven patients required revision of their ileostomies, three having had two revisions. This complication can often be avoided by everting the mucosa down to the skin. All of the patients who had ileostomies alone died, while those who had ileostomy with colectomy and proctosigmoidectomy in one, two or three stages survived.

The six deaths occurred in patients with far advanced disease who were operated upon either as an emergency, semiemergency, or as a last resort procedure. This report points up the fact that patients who are in good nutritional status can survive any operative procedure indicated. The recent enthusiasm for the one stage ileostomy with total colectomy and removal of the rectum is supported by the good results obtained in four cases.

Mere spontaneous revision should not confuse the picture of a chronically invalided patient with an increasingly rigid fibrous and almost useless bowel in which carcinoma may arise without the usual signs.

ALEXANDER ZABIN

THE CATASTROPHIC COMPLICATIONS OF ULCERATIVE COLITIS: CANCER, PERFORATION AND MASSIVE BLEEDING: Robert T. Tidrick and Robert C. Hickey. J. Iowa State M. S. 47:485-492 (Sept.), 1956.

Cancer, perforation and massive bleeding are considered as the three most prevalent catastrophic complications of ulcerative colitis.

While the incidence of colonic cancer as a complication of ulcerative colitis is not definitely known, evidence is presented suggesting that it is relatively high in those patients who have had prolonged active disease; therefore, they have suggested that surgical intervention be considered in those who have had unremitting activity for five or more years and who have a reasonably great life expectancy.

Intestinal perforation and massive bleeding as complications of acute ulcerative colitis or of violent exacerbations of the disease may be furthered by administration of adrenocorticotrophin (ACTH) or cortisone. The indications and difficulties incident to surgical therapy as a part of the emergency treatment in patients with perforation and hemorrhage are noted.

GLENN S. ROST

LACTOBACILLUS ACIDOPHILUS TABLETS IN THE THERAPY OF FUNCTIONAL INTESTINAL DISORDERS: Asher Winkelstein. Am. Pract. & Digest. Treat. 7:1637 (Oct.), 1956.

The author reports the use of this medication in the treatment of constipation, diarrhea, of a functional nature, mucous colitis, sigmoid diverticulitis, megacolon, and antibiotic diarrhea. The use in the latter would appear to be of value and should stimulate further investigation. It had no apparent effect on organic diarrheas such as ulcerative colitis.

ABE ALPER

LIVER AND BILIARY TRACT

SURGERY OF THE BILIARY TRACT: Richard B. Cattell and Kenneth W. Warren. New England J. Med. 255:698 (11 Oct.), 1956.

This survey is based on original and authoritative papers of the last five years with the authors' own clinical experience for comparison. The pancreatobiliary duct junction is discussed from the experience of Millbourn in 200 dissections and Sterling in 100 dissections. The notable conclusion is that it is only a common channel traversing ⅝ of the length of the papillae that would permit intraductal reflux. This occurred in approximately only 3 per cent of dissections. It is the impression of the authors that the common-channel theory in terms of the etiology of acute and chronic pancreatitis has been considerably overemphasized.

The question of oral cholecystography is next considered. Conclusions are derived from the study of several series that a high degree of diagnostic accuracy can be obtained with doses of 2 or 3 gm. of Telepaque, and it can be stated that nonvisualization of the gallbladder after 2 gm. of Telepaque is definitely indicative of biliary tract disease.

Intravenous cholangiography is considered the most significant advance in recent years in the study of the biliary tree. Ten minutes after intravenous administration of cholografin the hepatic and common ducts are visualized. Optimal visualization of the ducts occurs in 20 to 60 minutes. The gallbladder is visualized in from 30 minutes to 2 hours. Visualization of the ductal system occurs in 85 per cent of cases and could approach 100 per cent if there was no jaundice or depression of liver function. The test is not indicated when the bilirubin value is above 4 mg. per 100 ml. and when bromsulfalein retention is above 40 per cent. The optimal normal diameter of the common duct is given at 7 mm. in one series,—in another series the unobstructed ducts varied from 3 to 15 mm., whereas the obstructed ducts varied from 8 to 30 mm. There is an area of overlapping from 8 to 15 mm. for nonobstructed and obstructed ducts. This occurs in 57 per cent of cases and in these instances the mere size will not permit distinction regarding the presence or absence of obstruction. Opacification disappears at the end of 60 to 90 minutes in ducts up to 8 mm. whereas the larger ducts were opacified for 2 hours or more.

The controversial question of early or delayed surgery in acute cholecystitis is resolved by the authors handling each case as they meet it. They contend that the need for emergency surgery is rare, however, the case that enters the hospital with the diagnosis of acute cholecystitis seldom leaves the hospital without cholecystectomy.

JULES D. GORDON

CALCIFIED LIVER METASTASES: Josephine Wells. New England J. Med. 255:639 (4 Oct.), 1956.

Calcification in the right upper quadrant may lie in the kidney, adrenal gland, gallbladder, liver, or retroperitoneal area. Positioning, pyelography, and cholecystography, are of help in differentiating some of these calcifications. Liver calcification is quite rare and in hepatic metastases apparently is even more rare.

The author reports three cases of calcification in liver metastases. The primary tumor in two of these cases was proved to be in the sigmoid; in the other, according to the history and the pathological report, the primary lesion was probably in the colon although this was never proved. It is noteworthy that in this small series the calcification in the liver was very fine and was quite difficult to see on x-ray examination.

CHESTER S. SVIGALS

BOOK REVIEWS FOR GASTROENTEROLOGISTS

ESSENTIALS OF CLINICAL PROCTOLOGY—Third Edition: Manuel G. Spiesman, M.D., B.S., LL.D., F.I.C.P., Associate Professor of Proctology, Chicago Medical School, Chief of Proctology, Mt. Sinai Hospital Rectal Clinics, etc., etc. and Louis Malow, M.D., B.S., F.A.C.S., Associate in Surgery, Chicago Medical School, Proctologist, Grant Hospital, Rectal Clinic Mt. Sinai Hospital. 316 pages, illustrated. Grune & Stratton, Inc., New York, N. Y., 1957. Price $8.75.

The 3rd edition of "Essentials of Clinical Proctology", was brought up to date by the authors and is now a complete reference book on anorectal conditions. New chapters and material enhance the text. The illustrations are clear and describe, step by step, the procedures used in nonsurgical and surgical methods. The chapters on the injection treatment of hemorrhoids and ulcerative colitis make worthwhile reading as do those on pruritus ani, postoperative complications, amebiasis, polyps, coccygodynia and proctalgia fugax.

Diet, medical treatment and an extensive index add to the value of the monograph.

Physicians who treat anorectal conditions should not fail to add Spiesman and Malow's Essentials of Clinical Proctology to their library.

CORONARY HEART DISEASE. ANGINA PECTORIS; MYOCARDIAL INFARCTION: Milton Plotz, M.D., F.A.C.P., 353 pages, 107 illustrations. Paul B. Hoeber, Inc., New York, N. Y., 1957. Price $12.00.

Scores of articles have been written in recent years on coronary heart disease. While some of them are undoubtedly excellent, few, if any could be used to their full advantage by novice and expert alike. The great majority are either too technical for the beginner or do not contain sufficient information and research data for the specialist. This gap has been admirably bridged by Dr. Plotz' book: it serves equally well those in the extreme ends of the profession, as well as its mainstay, the general practitioner. In addition, there are well over one thousand bibliographical references to satisfy the requirements of the most profound worker in cardiology.

The book contains 21 chapters, starting with the basic principles, etiology, statistics, geographic and ethnic factors and the relation of coronary disease to lipid metabolism. The chapters following deal with symptomatology, clinical features, diagnosis, including the latest diagnostic methods used, such as ballistocardiography and vectorcardiography, the text being adequately augmented by the use of excellent graphs and diagrams. The latest and all-important Transaminase test used in the diagnosis of acute myocardial infarction is well presented. Of special importance to gastroenterologists is the discussion of the differential diagnosis between coronary disease and gastrointestinal conditions, especially hiatus hernia and gallbladder disease. The next chapters deal with prognosis and treatment, with an entire chapter devoted to anticoagulant therapy, allowing equal space to its ardent proponents, as well as to the more critical ones, who would use it only in well selected cases. Dr. Plotz steers a wise middle course. He prefers to give it—after excluding those with absolute contraindications—"to all patients for the first 3 days, discontinuing treatment if the prognosis seems good". This chapter also contains ample discussion of long term anticoagulant therapy with its indications and contraindications. In the next chapters the management of chronic coronary disease and angina pectoris is described, including their surgical treatment, describing the various methods aimed at revascularization and improved myocardial nutrition. Dr. Plotz displays a commendable level-headedness by not allowing his judgment to be influenced by over-enthusiasm which usually follows medical discoveries and innovations. He still believes that, while surgery undoubtedly plays a role and will probably play a still greater role in the future, the treatment for the present of the vast majority of cases of coronary disease is primarily medical.

In short, the reviewer recommends the book highly and he believes that it should have its place on the bookshelves of every student and practitioner of medicine.

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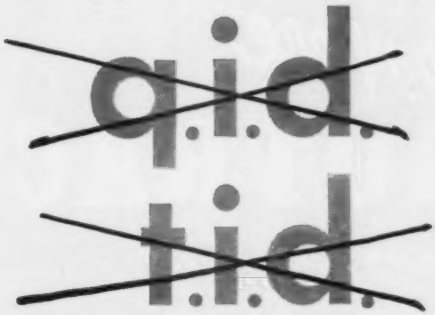

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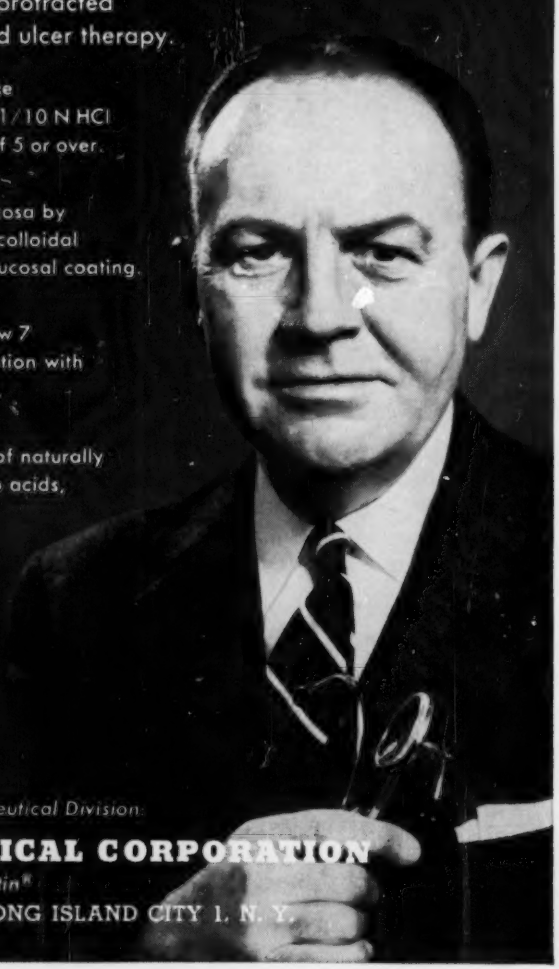

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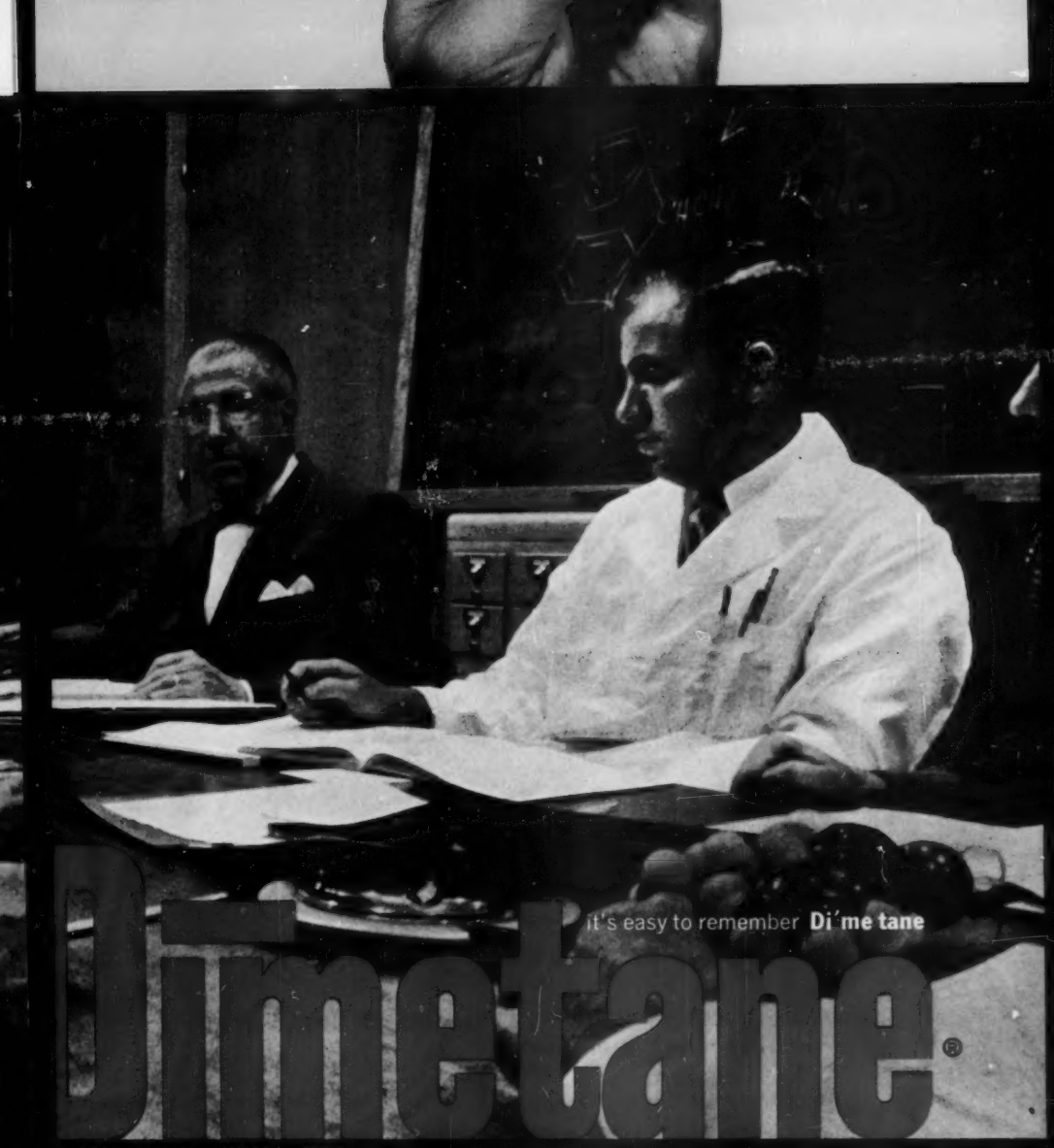
Total	37	15	13	7	2	Drowsiness (5) Dizzy (1) 16.2%

From the preliminary Dimetane Extentabs studies of three investigators. Further clinical investigations will be reported as completed

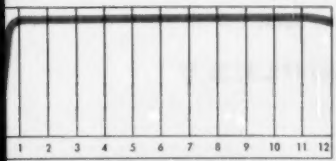


ANE® EXTENTABS® TABLETS ELIXIR

PARAHROMOLAMINE MALEATE

EXTENTABS 12 MG., TABLETS 4 MG., ELIXIR 2 MG. PER 5 CC.

blanket of allergic protection, covering 10-12 hours—with just one Dimetane Extentab »*DIMETANE Extentabs protect patient for 10-12 hours on one tablet.* Periods of stress can be easily handled with supplementary DIMETANE Tablets or Elixir to obtain maximum coverage.



Dosage:

Adults—One or two 4-mg. tabs. or two to four teaspoonfuls Elixir, three or four times daily. One Extentab q.8-12h. or twice daily. Children over 6—One tab. or two teaspoonfuls Elixir t.i.d. or q.i.d., or one Extentab q.12h. Children 3-6—½ tab. or one teaspoonful Elixir t.i.d.

A. H. ROBINS CO., INC.

Richmond, Virginia | Ethical Pharmaceuticals of Merit Since 1878

Robins

new paper[1] suggests 3 uses for DESITIN® ointment by colostomy patients

1 "In case of skin irritation around the colostomy" Desitin Ointment "under the dressing would be effective."

2 "to prevent possible stricture of the stoma at skin level" the patient should be taught to insert a gloved finger covered with Desitin Ointment.

3 The catheter used for irrigations "may be lubricated" with Desitin Ointment.

After ileostomy and colostomy Desitin Ointment affords *persistent* soothing, lubricant and healing properties in helping prevent, and clear up skin excoriation. Tubes of 1 oz., 2 oz., 4 oz., and 1 lb. jars.

WHY NOT REQUEST SAMPLES?

DESITIN CHEMICAL COMPANY
812 Branch Ave., Providence 4, R. I.

1. Breidenbach, L., and Secor, S. M.: Proper Handling of the Colostomy Patient, Amer. J. Surg. 93:50, 1957.

when tense living causes G.I. distress

When indigestion, pain, heartburn, belching or nausea is due to G.I. spasm

MESOPIN-PB

TRADEMARK

(Homatropine Methylbromide and Phenobarbital)

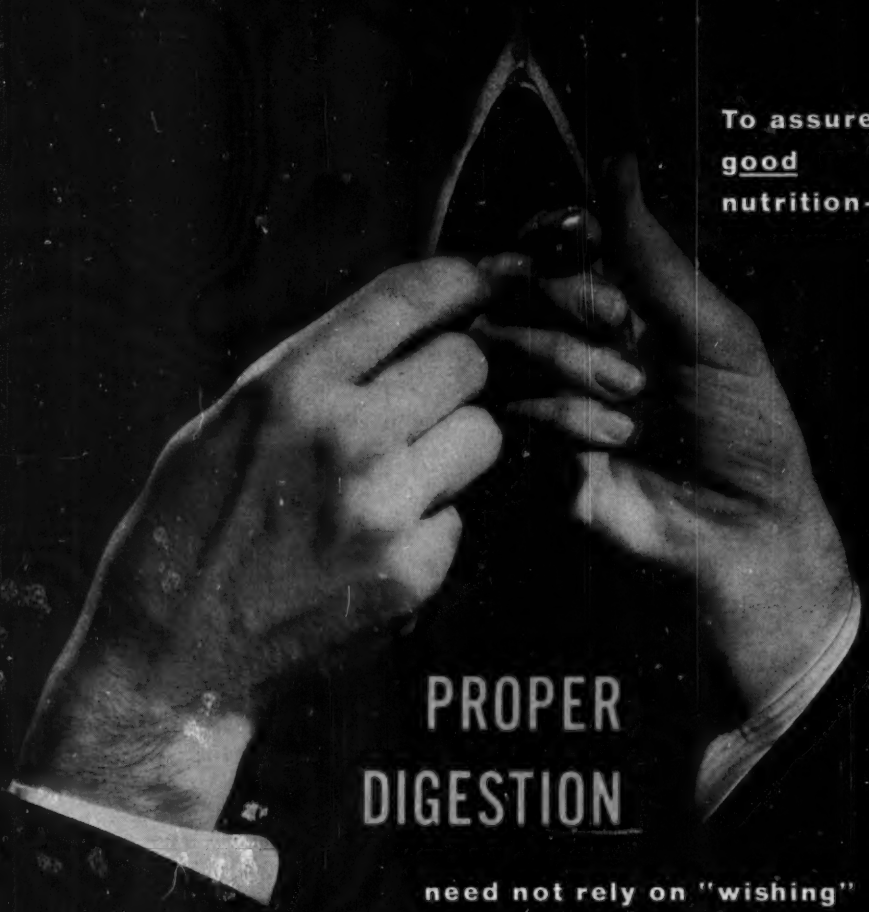
Provides the selective spasmolysis of homatropine methylbromide (1/30 as toxic as atropine) plus the sustained sedation of phenobarbital, with virtual freedom from undesirable atropine effects.

MESOPIN-PB contains 5 mg. MESOPIN (homatropine methylbromide) and 15 mg. phenobarbital in each green tablet. Also available as yellow elixir as well as MESOPIN Plain (without phenobarbital).

Samples? Write – ENDO LABORATORIES INC. Richmond Hill 18, New York

Endo®

the Colostomy Patient, Amer. J. Surg. 93:50, 1957.



To assure good nutrition—

PROPER DIGESTION

need not rely on "wishing"

Each double layered Entozyme tablet contains:

Pepsin, N.F. 250 mg.
—released in the stomach from gastric soluble outer coating of tablet.

Pancreatin, U.S.P. 300 mg.

Bile Salts 150 mg.
—released in the small intestine from enteric coated inner core.

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As a comprehensive supplement to deficient natural secretion of digestive enzymes, particularly in older patients, ENTOZYME effectively improves nutrition by bridging the gap between adequate ingestion and proper digestion. Among patients of all ages, it has proved helpful in chronic cholecystitis, post-cholecystectomy syndrome, subtotal gastrectomy, pancreatitis, dyspepsia, food intolerance, flatulence, nausea and chronic nutritional disturbances.

For comprehensive digestive enzyme replacement—

ENTOZYME

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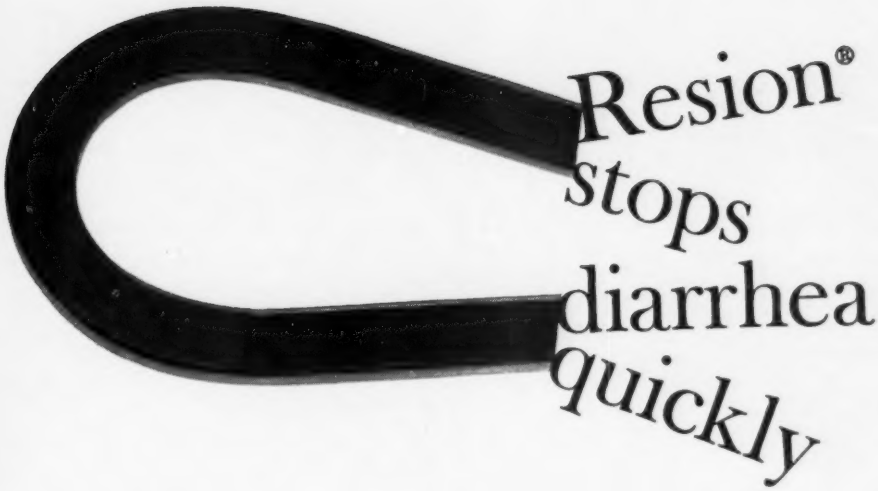

Resion acts instantly in the intestinal tract

by the unique electrochemical adsorptive action (anion exchange) of its resin component.[1] Insoluble and nontoxic[2], Resion removes noxious substances through electrochemical attraction—like a magnet. This action occurs instantaneously . . . as quickly as Resion and toxic acid molecules are within functioning range of chemical forces[1], —yet it leaves important amino acids, vitamins and minerals unaffected. With Resion, 86 of 90 patients had complete relief of diarrhea in 8 to 12 hours.[3]

For simple diarrhea: Resion, a combination of polyamine methylene resin and synthetic silicates.

For infectious diarrhea: Resion P-M-S, the Resion formula plus polymyxin, phthalysulfacetamide and the parabens.

References: 1. Martin, G. J.: Ion-Exchange and Adsorptive Agents in Medicine, Little, Brown and Co., Boston, 1953, P. 205. 2. Lichtman, A. L.: Exper. Med. & Surg. 9:90, 1951. 3. Gabroy, H. K., and Selsman, G. J. V.: Amer. J. Digest. Dis. 20:395, 1953.

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Old King Hal has many modern counterparts: executives who entertain . . . husbands who like "good eating," wives who serve "something different" . . . children who like "gooey" sweets. But for each the aftermath is often uncomfortable.

With Gelusil tablets or liquid, however, you quickly, soothingly relieve acute and chronic excessive gastric acidity! And Gelusil helps you manage the gnawing pain of peptic ulcer, too.

Gelusil stabilizes burning gastric acid within normal pH range, usually in minutes.

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